ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2021 November 9; 10(6): 112-199

Published by Baishideng Publishing Group Inc

WJCP

World Journal of Clinical Pediatrics

Contents

Bimonthly Volume 10 Number 6 November 9, 2021

World Journal of Clinical Pediatrics

Bimonthly Volume 10 Number 6 November 9, 2021

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INDEXING/ABSTRACTING

The *WJCP* is now abstracted and indexed in PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Toru Watanabe, Consolato M Sergi

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https://www.wjgnet.com/2219-2808/editorialboard.htm

PUBLICATION DATE
November 9, 2021

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World J Clin Pediatr 2021 November 9; 10(6): 112-123

DOI: 10.5409/wjcp.v10.i6.112

ISSN 2219-2808 (online)

REVIEW

Pediatrician-friendly perspectives on cognitive behavioral therapy for anxious youth: Current status and clinical implications for the next normal

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Author contributions: Friedberg RD is the only author.

Conflict-of-interest statement: Robert D Friedberg receives book royalties from Springer, Guilford, Routledge, John Wiley, and Professional Resource Press.

Specialty type: Pediatrics

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0

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Abstract

Pediatric anxiety disorders are common and often debilitating conditions. Cognitive is a psychosocial intervention that represents a potentially powerful antidote to these disorders. This article reviews data from treatment outcome studies, meta-analyses, and systematic reviews as well as from moderation/mediational investigations. The literature supports the efficacy, effectiveness, and durability of positive treatment outcomes for pediatric anxiety disorders. Recommendations for clinical applications are suggested.

Key Words: Pediatric anxiety; Cognitive behavioral therapy; Coping cat; Exposure

Core Tip: There are several core tips in this therapeutic advances article. First, while the state-of-the-science supporting cognitive behavioral therapy (CBT) for pediatric anxiety is very strong, proper delivery of genuine CBT by trained providers is fundamental to its success. Clinicians should provide CBT in a manner that balances flexibility within fidelity. Most importantly, exposure is an essential component to any CBT approach to pediatric anxiety disorders.

Citation: Friedberg RD. Pediatrician-friendly perspectives on cognitive behavioral therapy for anxious youth: Current status and clinical implications for the next normal. *World J Clin Pediatr* 2021; 10(6): 112-123

URL: https://www.wjgnet.com/2219-2808/full/v10/i6/112.htm

DOI: https://dx.doi.org/10.5409/wjcp.v10.i6.112

Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: May 3, 2021
Peer-review started: May 3, 2021
First decision: June 25, 2021
Revised: July 4, 2021
Accepted: September 1, 2021
Article in press: September 1, 2021
Published online: November 9, 2021

P-Reviewer: Shiina A
S-Editor: Fan JR
L-Editor: A
P-Editor: Yuan YY

INTRODUCTION

Anxiety disorders are highly prevalent conditions in child and adolescent populations [1-5]. Approximately 6.5% of youth worldwide suffer from anxiety disorders[4]. Anxiety disorders are also gateway disorders[3,6]. Thus, pediatricians frequently care for anxious youth in their practices and these young patients are frequently impaired. Effective psychosocial treatments are needed.

Fortunately, cognitive behavioral therapy (CBT) is widely regarded as the premier psychosocial treatment for pediatric anxiety disorders[7,8]. The approach has been empirically supported by meta-analyses, mediational and moderation studies, systematic reviews, randomized clinical trials (RCTs), controlled investigations, and case reports. Based on the aggregated results, both the American Academy of Child and Adolescent Psychiatry (AACAP) and the American Psychological Association (APA) see CBT as the gold-standard treatment. More specifically, AACAP[9] referred to CBT as the "front-line" psychosocial intervention for pediatric anxiety disorders. The APA defined CBT for anxiety disorders as a "well-established" treatment[10]. Reaching the "Well-Established" threshold means that CBT was evaluated by at least 2 RCTs indicating efficacy where the treatment outperformed pill placebo, psychological placebo, or another treatment comparison group. Further, the specific intervention must have been manualized and examined by two different research teams. Finally, the protocol is required to have demonstrated equivalence to another Well-Established treatment or two approaches studied in investigations with at least $n = 30$. In sum, the well-established threshold is a stringent criterion. While anxiety disorders are highly prevalent and impairing, CBT is a widely deployed and effective intervention.

In this pediatrician-friendly perspective, CBT basics are briefly summarized and the empirical literature supporting the approach is discussed. Results from treatment outcome evaluations examining the seminal Coping Cat program, data from the Child/Adolescent Anxiety Multi-Modal Studies (CAMS) along with findings from reviews and meta-analyses are delineated. Further, the impact of mediators as well as moderators are presented. Finally, the article concludes with clinical recommendations for the peri- and post pandemic period.

BASIC DESCRIPTION OF CBT FOR PEDIATRIC ANXIETY: THERE'S NOTHING LIKE THE REAL THING

CBT is a multi-component treatment paradigm is that is widely adopted[11-14]. Contemporary CBT with youth is increasingly adopting a modular approach to treatment (mCBT)[15-19]. In general, modular approaches identify the best procedures commonly found in many treatment packages/protocols and organize them into conceptual clusters. The techniques are grouped into particular units that share a purpose or function [*e.g.* orienting patients to treatment, cognitive restructuring (CR), *etc.*]. mCBT offers several compelling advantages including parsimony, reduced training burden, personalized/individualized care, and attractiveness to providers [15]. Typical modules include psychoeducation (PE), basic behavioral procedures (BBPs), CR, and exposure/experiments.

PE paves the way for the various intervention strategies. PE teaches patients as well as their families about anxiety disorders and treatment alternatives[20,21]. Moreover, PE enables genuine informed consent as well as increased help-seeking, collaboration, demystification, universality, empowerment, and hopefulness[18,22-25]. It may be delivered verbally or through books, pamphlets, video/audio recordings, internet sites, and mobile applications[17,18].

BBPs are based on "systematic application of conditioning principles to clinical disorders[26]." Typically, these procedures focus on acquiring and applying specific skills to particular problems[14]. BBPs include a stable of familiar approaches including relaxation, contingency contracting, and social skills training.

CR and rational analysis (RA) focus on re-engineering thought content and processes respectively[17,18,27]. Problem-solving, self-instructional, and self-talk techniques are classic CR procedures. A voluminous literature base exists that supports the use of CR methods[27-34]. RA procedures are more advanced methods and enjoy a long history in CBT[35-40]. "Analysis of meaning and attitudes exposes the unreasonableness and self-defeating nature of the attitudes[38]." Tests of evidence, reattribution, decastrophizing, and universal definitions are common techniques used in RA [38-40].

Exposure is seen as essential when treating anxiety disorders in youth[8,17,41-49]. Successful completion of exposure tasks involves young patients' undivided attention, use of coping skills, and persistence amid negative emotional arousal[50]. The exposure component in CBT treatment uniquely differentiates CBT from supportive treatment[45]. Approximately 88% of the strongest studies evaluating treatment outcome for anxiety disorders in youth incorporated exposure in their intervention protocol[46]. When exposure elements were absent from CBT treatment approaches for anxiety, the effects were significantly attenuated[42,49,51]. In a meta-analysis focusing on dismantling the effective components of CBT for anxiety disorders in youth that included 75 studies, in-session exposure resulted in larger effect sizes when comparing CBT to wait-list control groups[41]. Increasing the emphasis on in-session exposure over anxiety management strategies such as those procedures described in the basic behavioral tasks as well as the CR modules may improve CBT's efficacy[41].

Proper delivery and dosing of genuine CBT is crucial. There is data that clinicians self-identify as CBT practitioners, yet their in-session behavior does not resemble the true treatment approach[52]. Practicing flexibly with faithful adherence to CBT tenets is the current clinical watchword[11,53-55]. Competent CBT providers are seen as expert multi-taskers[56]. Consequently, they are able to balance faithful adherence to the model while making immediate adaptations in response to young patients' unique presentations[11]. Flexible applications of CBT enable real-time adaptations, matching treatment to individuals' psychological characteristics, and incorporating cultural vicissitudes into the intervention[53-55]. In this way relevance matching[57] is better achieved which facilitates building a more personalized treatment package.

TREATMENT OUTCOME STUDIES: COPING CAT

Coping Cat is a CBT protocol that is typically delivered in 12-16 sessions divided into two phases[12,58-60]. The classic FEAR plan punctuates the first 9 sessions. The feeling frightened component helps young patients monitor their physiological signs of anxiety. Identifying their catastrophic predictions defines the expecting bad things to happen part. Developing coping counter-thoughts and adaptive problem-solving strategies is the focus of attitudes and actions that can help. The fourth segment, results and rewards, teaches children to reward their productive coping efforts. Exposures and behavioral experiments make up sessions 10-16. During this stage, patients apply the skills acquired *via* the FEAR plan in various anxiety producing situations. Homework assignments called show that I can exercises are completed over the course of the Coping Cat protocol to facilitate treatment generalization and a sense of self-efficacy. The treatment package has been widely implemented in the United States and internationally[59,61].

Early RCTs evaluating the Coping Cat yielded very encouraging findings[62,63]. Coping Cat outperformed a wait-list control group in a RCT on several measures with young patients resulting in less symptoms, greater coping ability, and increased social skills[62]. Moreover, the gains showed durability with improvements holding up at 1 year[62] as well as 3.5 years later[64]. A subsequent RCT[63] also found similar positive results with 50% of patients being symptom-free at the end of treatment. These gains were sustained at 1 year[63] and 7.5 years after treatment[65].

Coping Cat was compared to an active treatment contrast condition (Humanistic Therapy) in a recent study including 133, 9-14 year old youth[45]. Although both treatments yielded similar acute response data, the CBT group was more likely to fully recover and no longer meet diagnostic thresholds at the end of treatment than counterparts receiving the Humanistic approach. Further, the patients in the CBT condition evidenced higher recovery rates at the 1 year follow-up point. The study authors'[45] concluded that CBT resulted in greater breadth and generalizability of treatment gains as well as more durability over time.

In an effectiveness study examining Coping Cat delivered by practitioners in a community setting rather than in a more controlled academic setting, participants in the treatment package outperformed wait-listed control group cohorts and the gains were maintained at 2 year follow up points[66].

Intolerance of uncertainty (IU) was targeted in a study examining Coping Cat's clinical promise[67]. IU is seen as an important mechanism of action in anxiety disorders. This study found that decreased IU from pre-post treatment was associated with lowered functional impairment, increased coping, and decreased anxiety severity. These results imply that focusing specifically on uncertainty in CBT for anxiety may improve outcomes.

Treatment outcome studies: The CAMS

The CAMS was the most wide-ranging RCT evaluating the use of CBT (Coping Cat) and Serotonin Selective Reuptake Inhibitors (SSRI, Sertraline) for the treatment of anxiety in youth[68,69]. The project involved 488 participants (7-17 years of age) across multiple sites and assessed outcomes at 12, 24, and 36 wk. The data indicated that after 12 wk, the CBT, SSRI, and CBT + SSRI conditions all outperformed the placebo group [68]. More specifically, 80.7% of youth in the combination, 59.7% in the CBT alone, and 54.9% in the singular sertraline treatment arm improved on the Clinical Global Impression Scale. A dismantling study of 279 participants enrolled in the CAMS project showed that anxious youth who received more sessions devoted to exposure demonstrated greater symptom reduction and functional improvement[8].

In a project examining response and remission rates, all three arms of CAMS (CBT, SSRI, COMBO) sustained their rates of improvement, however the superiority of the combination treatment did not persist at the 36 wk mark[69]. Extended long term gains were evaluated in a study of 319 youths[70]. Based on linear and quadratic growth models, CBT was associated with faster improvement, academic achievement, and greater life-satisfaction. These gains appear to endure for approximately 6.5 years.

The question of which treatment arm is best-suited for which patients was researched in another secondary data analysis[71]. The single treatments (CBT, SSRI) worked equally well for patients with lower levels of anxiety whereas the combined CBT + SSRI package was essential for symptom remission in patients with more severe anxiety. Additionally, low SES predicted poorer treatment response. Thus, it appears that the combination treatment is indicated for more distressed individuals who may be more financially challenged.

REVIEWS AND META-ANALYSES

An early review article concluded RCTs evaluating CBT spectrum approaches yielded positive treatment outcomes earning medium effect sizes[72]. In a later review of 24 RCT's with children and adolescents diagnosed with a variety of anxiety disorders, large pre-post differences were reported[73]. Additionally, rates of clinical improvement ranging from 60%-80% were found. Further, when a conservative benchmark of remission was applied, 50%-70% of patients claimed they were symptom free[73]. A recent comprehensive review evaluated multiple treatment paradigms for anxiety according to various levels[46]. The review concluded that CBT earned a large effect size and demonstrated durability of outcomes with diverse populations. Moreover, when applying another more stringent criteria such as functional improvement in patients, CBT was the only approach that met the Well-Established threshold. Children who received CBT were 3 to 7 times more likely to show improvement than cohorts in the passive control condition[74].

A variety of meta-analyses examining CBT's potential to reduce anxiety disorders have been conducted[75-78]. In a meta- analysis exploring the efficacy of CBT for anxiety disorders in youth, 11 meta-analyses incorporating 350 comparisons were evaluated[75]. The results yielded medium to large effect sizes for CBT compared to non-active controls [mean weighted effect size (d) = 0.76]. Further, the effect sizes were somewhat smaller when testing CBT *vs* active comparison groups (d = 0.40). Finally, when pre-post differences in anxiety for CBT were studied, large effect sizes were found (d = 0.88). When examining compete symptom recovery, another meta-analysis concluded 61 percent of youth show symptom remittance after a course of CBT[78].

A systematic review and meta-analysis including 115 studies covering 7719 patients with a mean age of 9.2 years showed that when CBT was compared to wait list comparison groups, CBT led to greater symptom reductions and remissions[77]. Moreover, the same meta-analysis found that attrition rates were lower in the CBT condition than the in pill/placebo contrast groups. Moreover there were less adverse events in patients receiving CBT than in counterparts who were in the medication groups (SSRI). These results appear to suggest that CBT is more well-tolerated by young patients than medication[79]. Finally, the combination of CBT with SSRIs was a stronger treatment than either mono-therapy alone[77].

CBT also demonstrates considerable promise when applied to anxious adolescents. Large pre-post differences, medium to large effects sizes, and encouraging remission rates were found. In particular, post-treatment remission rates ranged from 27%-35% and from 52 to 60 percent in various studies[73].

MODERATORS AND MEDIATORS

Examining moderator and mediator variables adds another dimension to treatment outcome studies. Moderation analyses can determine what treatment, for what type of patient, under which circumstances works best[80]. A moderator variable is defined as either a qualitative or quantitative construct that "affects the direction and/or strength of the relationship between an independent or predictor variable and a dependent or criterion variable[81]". Moderator variables represent pre-randomized characteristics that do not explain treatment effects but rather interact with them[82]. In general, moderator analysis examines performance of subgroups in certain conditions[80].

Conversely, mediators specify the mechanisms of change in dependent variables and speak to how or why effects occur[81]. Behavior change, especially decreased avoidance, is a powerful mediator of treatment outcome for anxiety disorders[83]. Negative cognitions especially future-oriented, catastrophic thoughts were also seen as significant mediating variables and homework assignments earned small to medium effect sizes[83]. Results for parental behavior and treatment alliance were deemed inconclusive as far as their contribution to outcomes[83].

Several studies based on the CAMS investigations identified some additional potential mediators. In a follow-up investigation including 488 youths, coping efficacy mediated clinical outcomes[84]. Perception of social threats mediated treatment response in a naturalistic follow-up evaluation of 319 young patients enrolled in CAMS[85]. Somatic symptoms mediated treatment outcome for the sertraline arm of the CAMS study[86]. The most consistent predictors of treatment response found across studies included type of primary anxiety disorder, severity of anxiety, co-morbidities, and parental psychopathology[82].

In an analysis of the CAMS data based on 488 young participants, no demographic variables moderated the clinical outcomes[87]. A recent comprehensive review evaluated research on moderator variables such as co-morbidity, presence of social anxiety, gender, age, race/ethnicity, parental involvement, parental psychopathology, family factors, therapist variables, and dose of therapy[83]. These investigators noted that treatment outcomes did not vary as a function of the severity of illness and regardless of pre-treatment severity, anxious youth demonstrated a similarly favorable treatment response. On the other hand, co-morbid conditions such as autism spectrum disorders, depression, and attention deficit disorder did moderate the outcome. They concluded gender and ethnicity did not significantly influence treatment outcome, indicating that male and female, as well as diverse youth, benefit similarly from CBT. Moreover, parental involvement in treatment and family factors were not seen as significant moderators. Parental psychopathology had some modest influence on treatment depending on the age of the child, with a stronger impact on outcomes for younger youth. Overall, the data on age of the patient was considered inconclusive. Finally, therapist variables such as flexibility and collaboration demonstrated moderating effect on treatment outcomes.

A number of reviews agree that demographic variables (*e.g.* biological sex, race/ethnicity, SES, *etc.*)[43,73,82] do not significantly moderate treatment outcome for anxiety disorders in youth. Nonetheless, there is some evidence that gender and ethnicity are correlated with differential attrition rates[60]. It could be argued that many of these studies are under-powered to detect significance, but this criticism is somewhat recently debunked[72]. The CBT procedures appear to be applicable to a wide range patients[83,87].

RECOMMENDATIONS

The literature reviewed tells a compelling story with multiple implications for clinical practice. The data supports CBT's effectiveness and efficacy as well as its wide applicability to diverse groups of young patients[8,45,62,63,67,83,87]. Additionally, CBT enjoys durable positive effects[64,65,69,70]. CBT is equally as effective as SSRIs but is associated with less adverse side effects[68,77,79]. Psychological distress characterized by anxiogenic cognitions and behavioral avoidance are apparently the most productive targets for intervention[2]. Perhaps most pivotally, the exposure component to treatment is essential to distinguish between more and less effective CBT as well as differentiate CBT from other systems of psychotherapy[8,17,41-51]. Simply, CBT for anxiety without exposure is a diluted approach[88].

The extant literature aids pediatricians in treatment planning. The findings of equivalence between SSRIs and CBT in treating anxious youth gives patients and

providers multiple choices. Either mono-therapy is suitable for these individuals, but CBT is associated with less adverse side effects. Pediatricians might consider starting less severely distressed patients on a course of CBT since it is associated with fewer side effects, track progress, and if indicated, augment the CBT with medication. For more severe presentations especially those with strong somatic complaints, the combination treatment seems best.

The world is currently in the midst of a devastating public health crisis caused by the coronavirus disease 2019 (COVID-19) pandemic. In general, pandemics are characterized by increased anxieties and worries[89-92]. Various authors believe the COVID-19 pandemic is a powerful trigger for health anxiety[93,94]. Hospital records in the United States document a startling increase by 24% and 31% in emergency room visits die to anxious symptoms for children and adolescents respectively[95]. Regrettably, the psychological sequelae do not appear to self-limiting[90]. They are here to stay.

Accordingly, ensuring the proper delivery of CBT to young patients is pivotal to meet the rising tide of cases, provide effective and efficient treatment as well as minimize clinical errors. However, there are relatively few clinicians practicing in treatment-as-usual settings who are trained to deliver a proper dose of evidence-based psychotherapies[96]. Unfortunately, many clinicians incorrectly self-label themselves as CBT clinicians[52,97-99]. In fact, when actual clinical practices were studied, few providers who self-labelled themselves as CBT oriented practitioners genuinely delivered a proper dose of CBT[52]. This finding is consistent with the phenomenon of "posing" as a CBT therapist rather than practicing as one[99]. Thus, attention needs to be regularly directed to the proper application of CBT with youth.

Clinicians are also well-advised to practice CBT in a faithful and flexible manner[53-55]. Patients typically arrive to clinics experiencing different family circumstances and living in diverse cultural contexts. Additionally, pediatric patients' predisposing characteristics and learning styles likely make them more or less receptive to varying therapeutic styles. For instance, some young patients may present to treatment with limited literacy. In these cases, clinicians are well-advised to rely on more concrete behavioral procedures such as exposure techniques. Additionally, scaffolding the cognitive demands to make the methods more accessible is recommended. Fortunately, there are many child-friendly iterations of traditional cognitive interventions available that are suitable for patients with limited literacy[11,16-18,47,58,60,61]. Perhaps, the attention alert CBT-oriented clinicians pay to working faithfully and flexibly partially explains the wide applicability of the approach.

Employing exposure based treatments for youth is a crucial task for clinicians. Exposure is underutilized in general[100-105] especially with younger children and children prescribed medication[8]. For instance, it was found that only 13% CBT oriented therapists used exposure based techniques[100]. In another study, a mere 40% of practitioners employed exposure procedures and these interventions accounted for only 1/5th of all clinical strategies utilized[103]. Further, exposure techniques were applied 19% of the time compared to CR (57%) and breathing exercises (53%)[105]. Finally, 48% percent of clinicians reported not implementing exposure due to lack of training[104]. In sum, continued and close attention to training clinicians in exposure-based treatments is necessary to fully equip practitioners with essential skills.

Multiple guidelines exist to guide clinicians' work with youth during exposure procedures[11,17,18,44]. Collaboration between clinicians and patients is essential during exposure. It is important to remember that exposure is done with rather than to patients. Children spearhead the exposure journey and the key for practitioners is to nurture young patients' willingness to encounter instead of avoid anxiety producing situations.

Exposure starts with PE and providing a rationale. Metaphors and analogies such as germ theory where immunity is often bolstered by exposure are helpful. Additionally, the use of videos or books where coping models (*e.g.* Bruce Wayne aka Batman surrounding himself with feared bats) approach their heretofore dreaded circumstances are other options. Graduated exposure is the preferred delivery mode. Accordingly, exposure hierarchies which include different successive steps (*e.g.* challenges) operationalized through collaboratively constructed Subjective Units of Distress (SUDS) (*e.g.*, 1-10, 1-100) are commonly employed. Patience by providers is recommended and a useful axiom for using a hierarchy is "start in the low-mid SUDS range and proceed slowly."

Exposures should be comprehensive and done repeatedly. In-session exposures should be completed several times and then at-home exposures are attempted regularly between appointments. Moderate to high levels of emotional arousal in response to in-session exposures are favored[106]. Further, the procedure should encompass cognitive, behavioral, physiological, emotional, contextual and inter-

personal elements of the anxiety response.

Developmental sensitivity and clinical creativity is pivotal when crafting exposures [11,16,17,44,53-55,58,60,61]. Rewards for successful efforts are strongly suggested for younger individuals. Game and playful exposures are especially engaging for pediatric patients. It is important to remember that the goal in exposure treatment is for new approach learning to occur[107]. Improved self-efficacy and greater self –control should result. Therefore, any exposure-based procedure should not be terminated before new learning emerges through either reductions in subjective distress, increased emotional tolerance, and/or greater approach behavior.

Finally, after the exposure is completed, clinicians and patients debrief the experience. Patients compare their predictions about what might happen to what actually occurred. They then craft their new conclusions and inferences based on the outcomes of the exposure.

The use of telehealth services has dramatically increased during the COVID-19 pandemic[108,109]. Virtual delivery of clinical services offers intriguing advantages and opportunities[110-112]. CBT provided *via* telehealth platforms is convenient and allows for interventions in young patients' home environment[110,112]. In particular, exposure done *via* telehealth allows for the clinician to process this experience with young patients while they engage in the procedure in their familiar context potentially adding to generalizability.

Finally, integrated pediatric behavior health care settings are well-suited to meet the cascading rate of new cases expected in the post-pandemic period. Ninety percent of children visit a pediatrician[113]. For many families, pediatric offices are the first stop for treating behavioral health complaints[114-116] Additionally, these care settings enable early identification and intervention[112,117-120]. Delivering CBT to anxious youth in pediatric settings increases access in familiar settings and enables better collaboration between pediatrician and behavioral health specialists.

CONCLUSION

CBT with anxious children and adolescents is a clear success story. Reaching the Well-Established threshold as well as equivalence with SSRI's is a major achievement. Extending CBT's reach into pediatric integrated behavioral health settings is an important next step. Broadening access to services from properly training clinicians will enhance the care of young people and sustain CBT practices.

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World J Clin Pediatr 2021 November 9; 10(6): 124-136

DOI: 10.5409/wjcp.v10.i6.124

ISSN 2219-2808 (online)

MINIREVIEWS

Corrosive upper gastrointestinal strictures in children: Difficulties and dilemmas

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Author contributions: Sarma MS contributed conceptualisation, intellectual inputs, final drafting; Tripathi PR contributed data retrieval, primary manuscript drafting; Arora S contributed intellectual inputs on surgical aspects.

Conflict-of-interest statement: The authors have no conflict of interest for this manuscript.

Specialty type: Pediatrics

Country/Territory of origin: India

Peer-review report's scientific

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Abstract

Children constitute 80% of all corrosive ingestion cases. The majority of this burden is contributed by developing countries. Accidental ingestion is common in younger children (< 5 years) while suicidal ingestion is more common in adolescents. The severity of injury depends on nature of corrosive (alkali or acid), pH, amount of ingestion and site of exposure. There are multiple doubts and dilemmas which exist in management of both acute ingestion and chronic complications. Acute ingestion leads to skin, respiratory tract or upper gastrointestinal damage which may range from trivial to life threatening complications. Esophagogastroduodenoscopy is an important early investigation to decide for further course of management. The use of steroids for prevention of stricture is a debatable issue. Upper gastrointestinal stricture is a common long-term sequelae of severe corrosive injury which usually develops after three weeks of ingestion. The cornerstone of management of esophageal strictures is endoscopic bougie or balloon dilatations. In case of resistant strictures, newer adjunctive therapies like intralesional steroids, mitomycin and stents can be utilized along with endoscopic dilatation. Surgery is the final resort for strictures resistant to endoscopic dilatations and adjunctive therapies. There is no consensus on best esophageal replacement conduit. Pyloric strictures require balloon dilatation , failure of which requires surgery. Patients with post-corrosive strictures should be kept in long term follow-up due to significantly increased risk of carcinoma. Despite all the endoscopic and surgical options available, management of corrosive stricture in children is a daunting task due to high chances of recurrence, perforation and complications related to poor nutrition and surgery.

quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 22, 2021
Peer-review started: February 22, 2021
First decision: June 5, 2021
Revised: July 30, 2021
Accepted: September 19, 2021
Article in press: September 19, 2021
Published online: November 9, 2021

P-Reviewer: Guo JT
S-Editor: Gao CC
L-Editor: A
P-Editor: Yuan YY

Key Words: Corrosive; Stricture; Children; Endoscopic dilatation; Adjunctive therapy; Surgery

Core Tip: Corrosive ingestion is a life-threatening problem in children. The sequelae are grave and tenacious. There are multiple dilemmas in the acute management of corrosive ingestion. Endoscopic dilatations have challenges and are the cornerstone in management of upper gastrointestinal strictures. Adjunctive therapies may play a pivotal role. Surgery is required in refractory cases.

Citation: Sarma MS, Tripathi PR, Arora S. Corrosive upper gastrointestinal strictures in children: Difficulties and dilemmas. *World J Clin Pediatr* 2021; 10(6): 124-136
URL: https://www.wjgnet.com/2219-2808/full/v10/i6/124.htm
DOI: https://dx.doi.org/10.5409/wjcp.v10.i6.124

INTRODUCTION

Burden of disease

Corrosive ingestion is one of the commonest causes of upper gastrointestinal strictures in children[1]. Worldwide, children represent 80% of all corrosive substance ingestion cases. The introduction of corrosives as household cleaning purposes has led to a rapid rise in accidental and suicidal ingestion in children. Majority are accidental[2,3] especially in children younger than 5 years who constitute 60%-80% of all pediatric corrosive ingestion cases[4,5]. Corrosives include both acidic and alkali substances. When these caustics come in contact with the skin or mucosa, they lead to variable extents of damage. In developed countries, corrosive injuries have decreased significantly due to strong efforts like childproof containers and biohazard labeling of caustics[6]. In developing countries, these substances are inexpensive, sold across the counter, unlicensed and often unlabeled for biosafety hazards[7]. The issue is worsened by poor literacy and unawareness. When it reaches the consumer, the caustics are stored in empty soft drink bottles and not kept out of reach of the children. Moreover, acid substances are transparent, resembling water. Younger children often fall prey to accidental ingestion out of temptation, curiosity or thirst[4]. As toddlers are verbally non-expressive, accidental ingestions may be unwitnessed and unreported till major symptoms arise. Suicidal and intentional ingestion is usually seen in dysfunctional adolescents with psychosocial trauma or in those with pre-existing psychiatric problems. In suicidal cases, caustic consumption is of large volume and symptoms are masked. Hence the cases present delayed with higher severity. Once acute complications are managed, strictures may develop at any site starting from the oropharynx, laryngeal inlet, esophagus or stomach, depending upon site of maximum contact. Strictures can be single or multiple, short or long and may involve multiple sites (*e.g.*, combined esophageal and pyloric strictures). The overall rate of esophageal stricture formation after caustic ingestion is reported between 2%-63%[4,8,9]. Rate of stricture formation varies with the severity of esophageal injury. Developing countries have mean death rate of 4.1% (0%-11.9%) due to corrosive ingestion[10]. Endoscopic dilatation and surgery are the mainstay for the management of strictures. From the emergency room at the time of first presentation to the management of stricture, there are many dilemmas regarding acute management, optimal timing of endoscopy, choice of dilatation (bougie *vs* balloon), use of adjuvant therapies, need of the surgery and long term prognosis of corrosive strictures. There is a paucity of literature on the management of corrosives in children. Practice varies from center to center with lack of uniformity. Therapeutic protocols or formulating guidelines are not available so far.

CLINICO-PATHOLOGICAL ISSUES

Commonly ingested corrosives are given in Table 1. Clinical manifestations are

Table 1 Commonly ingested corrosives in children

Acid	
Sulfuric acid	Batteries, industrial cleaning agents, metal plating, toilet cleaner
Hydrochloric acid	Solvents, metal cleaners, lime solvents, toilet and drain cleaners, muriatic acid, antirust compounds
Acetic acid	Pickling vinegar, vinegar spirit, wart solution
Phosphoric acid	Toilet cleaners
Oxalic acid	Paint thinners, metal cleaners, toilet cleaner
Alkali	
Sodium hydroxide	Grease/oil cleaners, drain cleaners, sink openers, oven cleaners, oil removers
Potassium hydroxide	Oven cleaners, washing powders, paint remover
Sodium carbonate	Soap manufacturing, fruit drying on farms
Sodium hypochlorite	Household bleaches
Ammonium hydroxide	General cleaner and grease remover
Miscellaneous	
Hydrogen peroxide	Surface and food cleaner
Potassium permanganate	Disinfectants, hair dyes

elaborated in Table 2. Alkaline substances have a higher viscosity, and hence remain in contact with esophageal mucosa for longer periods after ingestion. Alkali causes liquifactive necrosis and penetrate deeper into the tissue. Acids that have lower viscosity reach stomach faster, running along lesser curvature to reach the pylorus where there will be physiological stasis. Acid causes coagulative necrosis and deeper penetration is limited due to the same. Other factors that determine site and severity are chemical properties, contact time, contact surface area and urgency of referral. Many of the times, the nature and volume of corrosives are unclear from the history in children. Acids are available as pungent liquids; hence their intake is limited as soon as it is consumed accidentally. Alkalis are available both as liquids or solids (*e.g.*, soap and detergents). Since alkalis are tasteless, their consumption is higher before the patient realises the mistake. Retained solid alkali causes maximum injury to the oral mucosa, oropharynx and laryngeal inlet and lesser to lower esophagus and stomach. In the stomach, some of the ingested alkali may get partially neutralised by the gastric acid lowering the damage further. Ingestion of caustic after food cause a lesser degree of injury in the stomach due to lesser contact surface. Erroneous emergency interventions such as administering emetics and stomach wash cause repeated exposures of the caustic to the esophagus. Both alkali and acids are known to cause severe esophageal burns[11,12]. Initial corrosive injury causes an inflammatory response followed by thrombosis in arterioles and venules leading to ischemic necrosis [2]. Mucosal sloughing and bacterial invasion develop over four to seven days after ingestion warranting antimicrobial therapy. Granulation tissue and fibrin coat cover the ulcers. Ulcers extending beyond the muscle layer may cause perforation. The esophagus is physiologically devoid of serosa and allows the caustic damage to be exposed to the mediastinum. On day four, fibroblasts are recruited and repair of the damaged mucosa starts at day ten. Stricture usually develops by the third week and completes over the next few months[13]. As collagen deposition usually starts after two weeks, the strength of the injured tissue is poor in the first three weeks, contraindicating any intubation or endoscopic procedures. Spontaneous perforation of esophagus or stomach is usually encountered within the first 2 weeks of corrosive ingestion. From the third week onwards till the next few months, scar retraction leads to stricture formation and shortening of gastrointestinal tract. At this time, the pressure of the lower esophageal sphincter decreases and allows gastroesophageal reflux. Repeated acid exposure accelerates stricture formation[14]. In deeper burns (grade 2b and 3), fibrosis is usually complete by 3-6 mo, finally culminating into a stricture[15]. Strictures are hardly seen in grade 1 esophageal injury. Esophageal stricture rates in grades 2a, 2b and 3 are < 5%, 15%-68% and 75%-90% respectively[16, 17]. Diverticulae and deeper damage in the esophagus may result in tracheo-esophageal fistulae. Contraction of the body of the stomach causes hour glass appearance, decreased capacity and rarely fistulous opening into small or large bowel.

Table 2 Clinical features of corrosive ingestion

Symptoms of acute corrosive ingestion	
Organ system	
Skin	Burning sensation and pain on face, mostly perioral
Respiratory tract	Cough, difficulty in breathing, aphonia or dysphonia, chest pain, cynosis. Aspiration of large volume of corrosive may lead to endobronchial inflammation, necrosis and mediastinitis
Gastrointestinal tract	Oral burn, hypersalivation, nausea, vomiting (with or without blood), retrosternal and upper abdomen pain, dysphagia. Rarely perforation of gastrointestinal tract may happen and present with abdominal distension, tenderness and rigidity
Symptoms after gastrointestinal stricture formation	
Esophageal	Vomiting, dysphagia, hematemesis, acute obstruction due to food impaction at stricture site, growth failure
Pyloric	Non-bilious stale food vomiting, upper abdominal distension, growth failure

Antropyloric strictures cause gastric outlet obstruction. Proximal duodenal strictures are very rare. Compromise in nutrition leads to cachexia, dyselectrolytemia, apathy and poor quality of life. The above issues lead to a number of complications (Figure 1). Clinical, endoscopic and radiologic pictures of post-corrosive ingestion are shown in Figure 2.

DILEMMAS IN ACUTE CORROSIVE INGESTION MANAGEMENT

The flow chart for management of corrosive ingestion is shown in Figure 3. The first step is always to prioritize airway, breathing and circulation. Patients presenting with respiratory difficulty, dysphonia or aphonia need urgent airway management like endotracheal intubation and ventilation[18]. Urgent steroids are indicated in life-threatening laryngeal edema. However, there are many dilemmas and doubts which arise during acute management as well as while dealing with strictures.

What are the contraindicated practices?

Gastric lavage and induction of vomiting are common practices after accidental ingestion of corrosive[4,5]. In a survey performed recently in India, it was found that 57% of referred cases had history of induced emesis by the primary physicians[5]. Any effort of induced vomiting will lead to re-exposure of esophageal mucosa to the corrosive and increased risk of aspiration. Cold milk ingestion is not useful and may lead to aspiration and obscures an endoscopist's view. Blind insertion of a nasogastric tube for lavage or feeding may lead to mucosal injury and perforation. Another practice that is not recommended is the trial of neutralization with weak acid or base to decrease the effect of corrosive. The reaction of acid and alkali leads to an exothermic reaction which may cause added thermal burn to an already damaged tissue[18].

Is there any role of adjunctive pharmacotherapy?

Patients with grade 1 and 2a injury do not need any specific treatment, can be initiated on oral feeds and monitored closely. Children with grade 2b and 3 injuries need further treatment depending on clinical, endoscopic and radiological severity[7]. Antacids, H2 receptor blockers and proton pump inhibitors (PPIs) are prescribed in acute ingestion but their efficacies are not proven[2,19]. PPI is used in the majority of cases and may help by decreasing acid exposure to damaged tissue and prevention of stress ulcer formation[5]. Sucralfate which needs an acidic medium to activate provides a protective coating over the ulcers and may aid in delaying stricture formation[20]. However, the role of sucralfate in esophageal ulcers, alkali ingestion and in combination with PPI is debatable. There is no consensus as to how long acid suppression should be administered. In a questionnaire survey, it was found that most physicians arbitrarily prefer 4 week of acid suppression[5]. Antibiotics are not routinely prescribed in corrosive ingestion with grade 1 and 2a injuries. Since oral microbiota is a potential source of infection, injuries higher than grade 2b may merit antibiotic therapy. A combination of gram positive (for oral microbiota) and gram negative cover (gastrointestinal microbiota) is optimal. Optimal duration of antibiotic is not defined but it is preferable to use for 1-2 weeks for an uncomplicated injury. Syrups and suspensions are preferred over tablets and capsules. In a suspected or

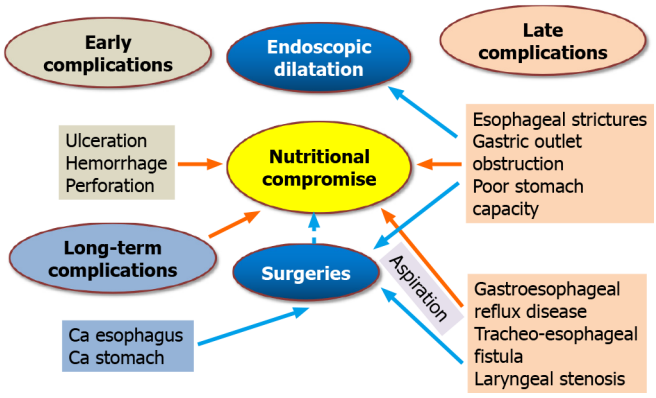

Figure 1 Complications in gastrointestinal system due to corrosive injury.

proven perforation, it would be prudent to add an anaerobic cover. Additional situations meriting antibiotic therapy are aspiration pneumonia, high grade fever and suspected bacteremia[21]. Theoretically, steroids have been potentially considered for use in early post-corrosive ingestion to decrease inflammation and lowering stricture formation. However steroids have not shown consistent improvement in the outcome [22]. In adults, steroids have been associated with higher mortality. In children, an exceptional situation to use steroids is grade 2b injury. Usta *et al*[23] showed in a randomized controlled trial that early use of high dose steroids (1 g/1.73 m^2 per day for 3 d) in grade 2b injuries lead to decreased stricture formation in follow-up. There is no evidence of improvement in other grades of injuries[7,23].

What is the indication and timing for early endoscopy?

In acute caustic ingestion, esophagogastroduodenoscopy (EGD) is the investigation of choice to ascertain the grade of mucosal injury. Esophageal injury is graded as per Zargar classification[24] as shown in Table 3. Endoscopy is best performed within the first 48-72 h of corrosive ingestion after initial stabilization. After 72 h, the injured areas become soft, edematous and friable. There is an increased risk of perforation during the EGD. EGD should be performed gently preferably with a thin (5.5 mm) endoscope, minimal air insufflation and under proper sedation. Blind advances and biopsies are not recommended. Negotiation beyond a charred esophagus to assess the stomach may be a daunting task. Oral or skin injuries are unreliable indicators of esophageal or stomach injury. In a large retrospective study by Doğan *et al*[25], 61% of children with esophageal injury on EGD had no oral burn. Betalli *et al*[26] in a multicentre study found that severe esophageal burns correlate well with symptoms. Risk of esophageal damage increased only with increasing severity of symptoms and signs. Hence the authors concluded that endoscopy can be avoided in asymptomatic patients with accidental ingestion[26]. European Society of Gastrointestinal Endoscopy and the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) 2017 guidelines agree, EGD can be withheld if the child is asymptomatic without any oral symptoms (drooling, hypersalivation or oral ulcers). However, in such cases, close vigilance is required for the development of delayed symptoms[7]. EGD is mandatory in adolescents with suicidal intent who may mask symptoms. The real dilemma of endoscopy arises in delayed presentation or referral (after 72 h). Since the tissue is most friable between days 3 to 21, diagnostic endoscopy is best avoided during this period where expertise and resources are limited. In the author's opinion, an endoscopic assessment may be daunting in this period, best reserved for tertiary care centers where appropriate endoscopes and expert endoscopists are available. Questionnaire surveys reveal that 90% prefer endoscopy between days 1-5, 70% agree that it should be deferred between days 6-21 and 50% agree that endoscopists should not venture beyond a charred area[5]. After 3-4 wk, fibrosis fully sets in making it conducive once again for endoscopic assessment of the stricture.

What is the role of radiology in acute management?

Chest X ray is usually performed in an acute setting[5] and may show mediastinal air in case of esophageal perforation. Computed tomography (CT) scan is a non-invasive test and can be used to ascertain the severity of injury and the need for surgery in complicated cases. Lurie *et al*[27] in a study on adult subjects concluded that CT tends to underestimate the severity of corrosive ingestion compared with endoscopy. CT

Table 3 Zargar classification for corrosive esophageal injury

Zargar classification	
Grade 0	Normal examination
Grade 1	Edema and hyperemia of the mucosa
Grade 2	
2a	Friability, hemorrhages, erosions, blisters, whitish membranes, exudates and superficial ulcerations
2b	Grade 2a plus deep discrete or circumferential ulceration
Grade 3	
3a	Multiple ulcerations and areas of necrosis (areas of brown-black or grayish discoloration were taken as evidence of necrosis)
3b	Small scattered areas of necrosis; extensive necrosis

scan had higher specificity but lesser sensitivity in ascertaining severity of injury in acute corrosive ingestion. The sensitivities of endoscopy in grades 2b and 3 injuries to predict mortality and emergency laparotomy were 1 and 0.8 while it was 0.4 and 0.28 for CT scan. The specificities were 0.38 and 0.37 for endoscopy while for CT scan the specificities were 0.94 and 0.93, respectively. CT scan can additionally show pulmonary infiltrates, features of mediastinitis and perforation[27]. A contrast study is carefully considered and performed only if indicated. Barium is ionic, may lead to chemical pneumonitis due to aspiration or tracheoesophageal fistula. Ingestion of barium also limits endoscopy if retained in luminal stasis. Hence a non-ionic contrast is preferred though the quality of study may be poor.

Should a nasogastric tube be preemptively placed for stricture prevention?

The pre-emptive placement of a nasoenteric tube is controversial. Though it may maintain patency of the esophageal lumen, the tube itself could worsen or contribute to complications. The tube may facilitate greater acidic reflux, delay mucosal healing and cause long strictures. Blind insertion could cause esophageal perforation. Should a tight stricture develop, positioning a tube has the advantage of providing a lumen for dilatation. Experimental studies were performed on rabbits with caustic esophageal burns. One group was treated with a silicone tube was placed immediately after causing the burns, while an untreated group was observed for the natural course of the burn. On day 22, an esophagectomy was performed on all animals. Histopathologic Damage Score and wall thickness were similar in both groups. Stenosis Index and lumen diameter were significantly lower in the treated group than the untreated group. It was concluded that an early placement of an intraesophageal tube with a solid dilator prevents stenosis formation and does not produce greater tissue damage [28]. To limit acid reflux it would be prudent to add an acid suppressant in the presence of a nasogastric tube.

What are the difficulties in sustaining nutrition?

Maintaining nutrition is a challenge in the first 3-4 wk. Nutritional compromise is anticipated due to odynophagia, multiple hospital admissions and overcautious management to prevent perforation. Adequate calories should be provided due to a high catabolic state. In rabbits models, it was found that weight gain is significantly higher after 22 d of caustic ingestion in those animals with nasogastric tubes[28]. Nasoenteric tubes must be placed under endoscopic or fluoroscopic vision. A nasojejunal tube is preferred in those with gastric injuries but may be challenging to place endoscopically especially through an inflamed pylorus. A safer alternative is to consider a gastrostomy tube in an isolated esophageal injury and a jejunostomy tube in gastric injury. Energy dense liquid and semisolid feeds are ensured in tube feeding. Parenteral nutrition is rarely required except for the patients with perforation and shock.

DIFFICULTIES IN MANAGEMENT OF CORROSIVE STRICTURES IN CHILDREN

Once the patient develops a symptomatic stricture, serial endoscopic dilatation is the

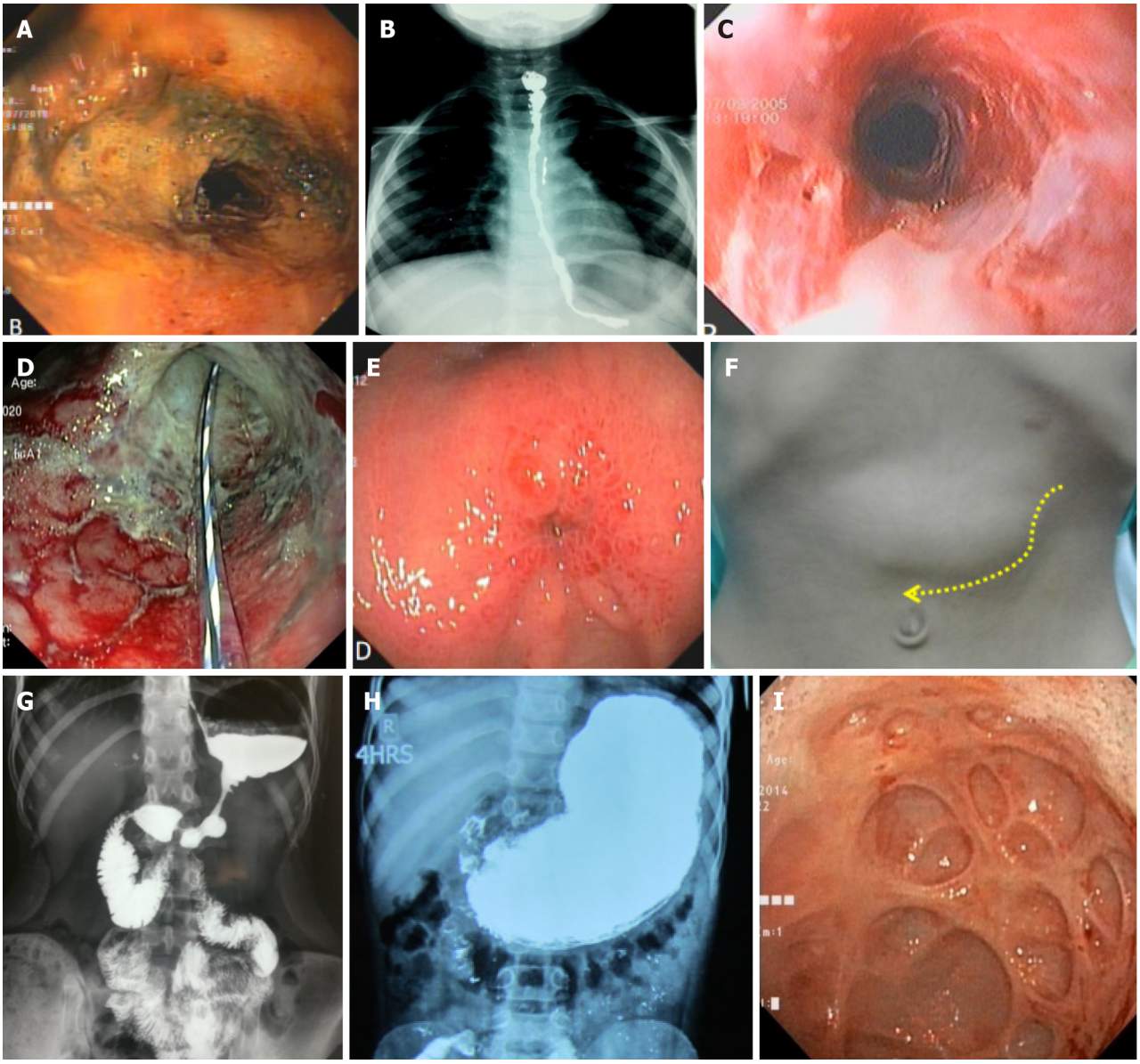

Figure 2 Clinical, endoscopic and radiological images of corrosive injury in children. A: Endoscopic view of corrosive injury of esophagus (areas of necrosis); B: Barium swallow study showing long esophageal stricture; C: Endoscopic view of esophagus after initial healing; D: Endoscopic view of post-acid ingestion antropyloric injury with transpyloric tube *in situ*; E: Endoscopic view of pyloric stricture; F: Dilated stomach in a patient with pyloric stricture; G: Barium meal follow-through study showing corrosive stricture involving body and prepyloric region (Hour-glass appearnce); H: Barium meal follow through study showing post-corrosive pyloric stricture; I: Endoscopic view of diverticulae in stomach in pyloric stricture.

mainstay of therapy to restore the previous anatomy and preserve the normal physiology. A barium study is indicated as a road map prior to endoscopy. The techniques of endoscopic dilatation are taken on a case-to-case basis depending on length, site, diameter, tortuosity and complexity of the stricture. A combination of thin and regular endoscopes may be required for assessment and procedures. Intubation may be a major issue in those with laryngeal stenosis. Unintubated patients are at significant risk of respiratory compromise during the procedure. Surgical therapy may be required for feeding purposes along with dilatation, to manage complications of endoscopic dilatation like perforation and for strictures resistant to endoscopic dilatation.

Should we use a bougie or balloon for endoscopic dilatation?

Strictures can develop as early as 3 weeks. Endoscopic dilatation is done every 2-3 weekly intervals and numbers of dilatation vary widely depending on the anatomy of the strictures. Endoscopic dilatation should be performed by a trained gastroenterologist under general anesthesia and with surgical backup. The first dilemma faced is, the choice of method for dilatation *i.e.*, bougie *vs* controlled radial expansion (CRE)

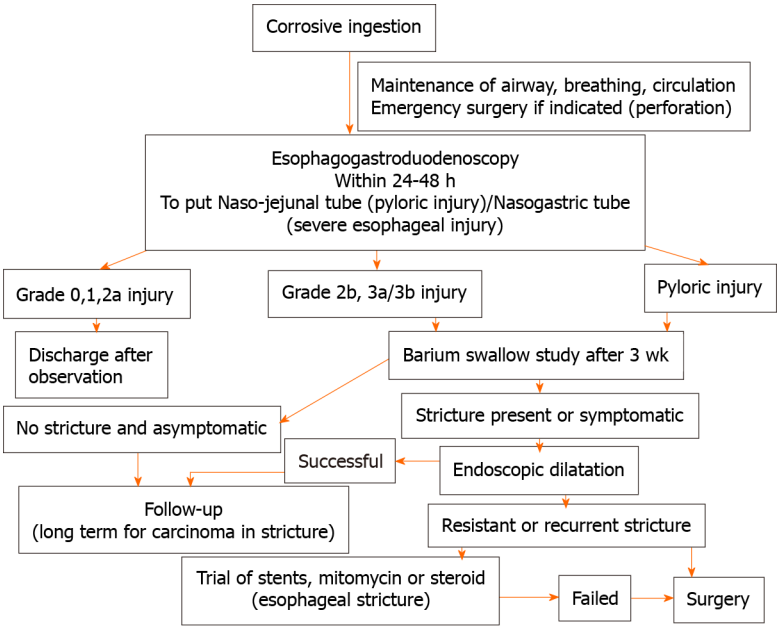

Figure 3 Flowchart for management of corrosive ingestion and upper gastrointestinal strictures.

balloon in an esophageal stricture. Bougie dilates the stricture with a tangential pressure while the CRE balloon asserts a radial pressure over the stricture. Bougie is a better option for multiple or long tortuous strictures while the balloon is preferred for single short strictures[29]. But practically, there are other factors also which influence the final decision like the experience of the endoscopist with both methods, availability of endoscopic accessories and financial constraints[5]. Bougie can be reused multiple times, lowering the overall cost of treatment. There are no head-to-head comparative studies between balloon and bougie. Balloon dilatation is found safe with variable success of 14%-100%[17,30]. Successful dilatation with bougie is 50%-96%[29,31]. It should also be kept in mind that thinner endoscopes have a limited channel length for balloon accessories. Softer guidewires than metallic ones are preferred to negotiate inflammed strictures. In tortuous strictures, optimal positioning of the patient and repeated gentle attempts are required for negotiation. Navigation is often aided by hydrophilic Terumo guidewire. Over the guidewire balloons are preferred if the anatomy of the lumen is uncertain.

Are corrosive esophageal strictures more resistant to dilate?

Of all benign esophageal strictures in children, corrosives are the most challenging to dilate due to the intense fibrosis and complexity. Corrosive strictures require a higher number of sessions of dilatation, have a higher risk of dilatation-related complications and may need surgical therapy more often as compared to other etiologies like post-trachea-esophageal fistula repair and peptic strictures[29,31]. The main complication of dilatation is perforation which is reported from around 2.5% to as high as 50%[31-33]. Other reported complications of dilatation are mediastinitis, lung abscess, empyema, pericardial effusion, sepsis and death.

When should we begin stricture dilatation?

Another dilemma is timing to start dilatation *i.e.* early *vs* late dilatation. Gün *et al*[32] compared patients who underwent early dilatation starting from 3rd week after corrosive ingestion *vs* patients who underwent late dilatation after 6-12 wk of corrosive ingestion. Children with late dilatation of stricture had a poorer response (25% *vs* 65%) along with higher rates of perforation (50% *vs* 21%). None of the patients with late dilatation recovered within 1 year period while 60% with early dilatation improved within the same time period[32]. Patients who are referred late often have a resistant stricture due to extensive fibrosis over time[2]. In a study by Contini *et al*[33], patients who were started on dilatation late (> 6 wk) had recurrence of strictures in 73% *vs* 30% in timely dilatation group ($P < 0.01$).

How to manage refractory esophageal strictures?

ESPGHAN guidelines for endoscopy have defined refractory and recurrent strictures as an anatomic restriction because of cicatricial luminal compromise or fibrosis that results in dysphagia in the absence of endoscopic evidence of inflammation. This may be defined in two clinical settings. Firstly there may be an inability to successfully remediate the anatomic problem to obtain age-appropriate feeding after a maximum of 5 dilation sessions (refractory) with maximal 4-week intervals. Secondly, there may be an inability to maintain a satisfactory luminal diameter for 4 week once the age-appropriate feeding diameter has been achieved (recurrent)[7]. In this subgroup of patients, the following options can be utilized before surgery.

Intralesional steroids: Intralesional steroid injection increases the effect of dilatation by inhibiting inflammatory response to injury, decreases collagen synthesis and cross-linking at the stricture site. Bhan *et al*[34] published data of 32 children with resistant strictures where Triamcinolone acetonide was injected in four quadrants prior to dilatation. 92% of patients with short strictures improved completely. None of the patients with long stricture (> 3 cm) had a resolution of dysphagia and all required esophageal replacement. A meta-analysis of 6 randomized control trials including 176 adult patients with benign esophageal stricture found that intralesional steroid therapy decreased stricture formation rate along with the requirement of endoscopic dilatations without an increase in complications[35].

Mitomycin: Mitomycin is an antineoplastic drug that inhibits cell division and fibroblast proliferation. A mucosal tear during dilatation heals with fibrosis. Hence mitomycin is used to limit this process and augment the effect of dilatation. Mitomycin soaked gauze (0.4 mg/mL) is applied over the stricture after dilatation for 3-4 min[36, 37]. Sweed *et al*[37] compared 18 children who underwent mitomycin injection with dilatation *vs* 12 children with routine dilatation. Results suggested that between the two groups, there were no major differences in the number of dilatations. However, there was a significant improvement in dysphagia in the mitomycin group. In another double-blind, randomized, placebo-controlled trial, the mitomycin group had complete resolution of stricture in 80% of patients as compared to 35% in the non-mitomycin group[38]. Méndez-Nieto *et al*[36] compared patients treated with mitomycin (n = 16) with a retrospective cohort of steroid-treated patients (n = 34). Mitomycin group required significantly less number of dilatation sessions [4.5 (3-8) *vs* 11 (4-24), $P < 0.01$].

Stents: The use of esophageal stents in children is still evolving and experience is limited. Resistant caustic strictures are the most common indication of stent placement in children[39]. Zhang *et al*[40] used nitinol-alloy self-expanding esophageal stent in eight children (2-12 years). Stents were deployed for 1-4 weeks. Stent migration occurred in one patient while two patients required further dilatation. None of the patients had any severe side effects. The use of stents in children is limited due availability of age-appropriate sizes and significant chances of migration. It is not possible to place stents in patients where stricture starts from the upper esophagus or from the pharyngeal inlet.

ESPGHAN guidelines suggest the use of temporary stent placement or application of topical mitomycin following dilation for refractory esophageal stenosis rather than routine use of intralesional steroids for refractory esophageal stenosis in children. There is a theoretical possibility of induction of dysplasia after mitomycin application although there is no proven evidence yet[7].

When is surgery indicated in esophageal strictures?

Surgery is the last resort for recurrent or refractory corrosive esophageal strictures. The optimal time for reconstruction is 6-12 mo post corrosive ingestion. The waiting period is beneficial for the final arrest of the progression of stricture (length, level and tenacity) and optimization of nutritional status. The major controversy in the surgical management of corrosive esophageal stricture is resection *vs* bypass. Currently majority of the surgeons prefer bypass since there is a lesser incidence of malignancy in the residual esophagus and lesser morbidity and mortality as compared to resection. Choices of esophageal replacement are gastric advancement/pull-up, colonic interposition and jejunal interposition. There is no consensus on the ideal replacement for the esophagus. The jejunum is not a preferred conduit because of its limited length. Free jejunal grafts may be used to bridge short defects after excision of localized esophageal stricture. Colonic interposition is a complex surgery requiring multiple anastomoses and affected by issues such as colonic redundancy. However,

colon is a favourable option because of the abundant vascularity and space of the lumen. Two options in colonic interposition are a right colon or a left colon conduit. The choice between these two is still debated. Gastric pull-up is comparatively a simpler surgery but it is dependent on the availability of a healthy stomach which may be partially involved or difficult to assess in corrosive ingestion. Routes available for conduit placement are posterior mediastinum, retrosternal and subcutaneous. The subcutaneous route is less preferred because of poor cosmesis. The retrosternal route is most commonly used in corrosive esophageal stricture as the native esophagus is left in situ. Colonic and gastric replacements both have shown good outcomes [21,41,42]. Studies have shown that there are no significant differences in terms of early complications (cervical anastomotic leaks, vocal cord palsy, and pulmonary complications) in colonic interposition or gastric pull-up[43]. Long term outcomes of these two procedures are also comparable. Overall complications of surgery include anastomotic leak, wound infection, graft redundancy, conduit failure and anastomotic strictures. Endoscopic dilatation may be required for anastomotic strictures[41,44].

What are the challenges in pyloric stricture management?

Acute caustic ingestion causes pylorospasm which increases the duration of contact in antrum and pylorus leading to antropyloric strictures. Adequate gastric decompression is recommended prior to endoscopy to reduce the volume of retained gastric juices. Antral strictures may appear as a pseudopylorus. In the authors' experience, an abnormally dilated stomach alters the usual endoscopic technique of negotiation along the lesser curvature to reach the pylorus. In a contracted stomach, pyloric strictures are often superiorly and eccentrically located than the usual position of pylorus surrounded by a "bird feet appearance" around the narrowing. These strictures are best identified on retroflexion with right-ward deflection of the endoscope. Multiple diverticulae are often misleading in identifying the real pyloric stricture, especially if the lumen is pin-hole in caliber. Blind negotiation of the guidewire may be catastrophic. In the first endoscopy, considerable attempts may be required to negotiate the guidewire. Increased friability of mucosa may lead to considerable bleeding and further edema of the opening. Balloon dilatation is the primary endoscopic procedure of choice. In very narrow strictures, a graded dilatation with biliary balloons is followed by CRE balloons. Unlike esophageal strictures, the bougie is not an option for pyloric strictures and there is limited experience with other adjunctive therapies like steroid and mitomycin in children. In earlier days, surgery was the primary mode of treatment for pyloric strictures. Various surgical options are gastro-jejunostomy with or without vagotomy, pyloroplasty, or antrectomy with Bilroth I anastomosis[45]. One important consideration is that retrocolic gastrojejunostomy should be avoided as it increases the technical difficulty or sometimes it precludes future colonic bypass by interfering with the middle colic vascular arcade. Patients may require repeat surgery due to anastomotic stricture although the incidence is low and patients do well in long term follow up[46,47].

With increasing endoscopic experience, surgery can be avoided especially if successive endoscopic dilatation attempts are successful[48]. This ensures restoration of normal anatomy and sustenance of the physiological outflow.

LONG TERM GASTROINTESTINAL COMPLICATIONS

There are a few other sequelae of corrosive ingestion which increase morbidity in addition to stricture formation.

Gastro-esophageal reflux disease

Cicatrization due to fibrosis in the esophagus leads to gastroesophageal reflux disease. Repeated acid exposure may lead to additional peptic stricture. These subgroups of patients require long term acid suppression for successful endoscopic dilatation[49].

Dysmotility

Corrosive injury and resulting fibrosis may damage the enteric plexus in the esophagus and stomach leading to esophageal dysmotility and gastroparesis respectively. Cicatrized stomach leads to issues of gastric accommodation and antral milling effect of chyme. These complications add to the existing symptoms of dysphagia, gastric outlet obstruction and may lead to persistence of symptoms even after adequate dilatation[50].

Risk of neoplasia

The incidence of esophageal carcinoma can be significantly higher in patients with corrosive ingestion as compared to the general population[51]. Carcinoma develops mostly at the site of stricture. Endoscopic dilatation or surgery does not prevent the development of carcinoma. Development of carcinoma may range anywhere from 1 to 7 decades after corrosive ingestion[52]. Change or onset of new symptoms in a patient with the past history of corrosive ingestion may be an indicator of carcinoma esophagus.

CONCLUSION

Corrosive ingestion is a common and preventable cause of esophageal and gastric injury in children. Development of stricture in the upper gastrointestinal tract is associated with prolonged morbidity, the need for long-term therapy and procedure-related complications affecting the quality of life in children. Despite many daunts and dilemmas in management, the clinical outcome is generally rewarding with endoscopic dilatations. Newer adjunctive therapies may decrease the need for surgery although for resistant and recurrent strictures. Even after the resolution of symptoms these patients should be kept on long-term follow-up. There is a need for further large volume studies regarding the efficacy and safety of newer adjunctive therapies. Long-term follow-up studies are required to evaluate stricture and management-related complications in children.

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2021 November 9; 10(6): 137-150

DOI: 10.5409/wjcp.v10.i6.137

ISSN 2219-2808 (online)

MINIREVIEWS

Beyond kidney stones: Why pediatricians should worry about hypercalciuria

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Author contributions: Penido MGMG and Tavares MS contributed equally to the conception and design of the study, the acquisition and interpretation of data, and the drafting and critical revision of the article.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Specialty type: Pediatrics

Country/Territory of origin: Brazil

Peer-review report's scientific

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Abstract

The incidence of urolithiasis (UL) is increasing, and it has become more common in children and adolescents over the past few decades. Hypercalciuria is the leading metabolic risk factor of pediatric UL, and it has high morbidity, with or without lithiasis as hematuria and impairment of bone mass. The reduction in bone mineral density has already been described in pediatric idiopathic hypercalciuria (IH), and the precise mechanisms of bone loss or failure to achieve adequate bone mass gain remain unknown. A current understanding is that hypercalciuria throughout life can be considered a risk of change in bone structure and low bone mass throughout life. However, it is still not entirely known whether hypercalciuria throughout life can compromise the quality of the mass. The peak bone mass is achieved by late adolescence, peaking at the end of the second decade of life. This accumulation should occur without interference in order to achieve the peak of optimal bone mass. The bone mass acquired during childhood and adolescence is a major determinant of adult bone health, and its accumulation should occur without interference. This raises the critical question of whether adult osteoporosis and the risk of fractures are initiated during childhood. Pediatricians should be aware of this pediatric problem and investigate their patients. They should have the knowledge and ability to diagnose and initially manage patients with IH, with or without UL.

Key Words: Children; Adolescents; Hypercalciuria; Bone mineral density; Kidney stone

quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 26, 2021
Peer-review started: March 26, 2021
First decision: July 27, 2021
Revised: August 8, 2021
Accepted: October 31, 2021
Article in press: October 31, 2021
Published online: November 9, 2021

P-Reviewer: Poddighe D
S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

Core Tip: The incidence of pediatric urolithiasis is increasing, and hypercalciuria is its leading metabolic risk factor. The reduction in bone mass has already been described in hypercalciuric children, and the precise mechanisms of bone loss or failure to achieve adequate bone mass remain unknown. The peak bone mass is achieved by late adolescence, peaking at the end of the second decade of life. This accumulation should occur without interference. The bone mass acquired during childhood and adolescence is the major determinant of adult bone health. Pediatricians should have the knowledge and ability to diagnose and manage pediatric patients with idiopathic hypercalciuria.

Citation: Penido MGMG, Tavares MS. Beyond kidney stones: Why pediatricians should worry about hypercalciuria. *World J Clin Pediatr* 2021; 10(6): 137-150
URL: https://www.wjgnet.com/2219-2808/full/v10/i6/137.htm
DOI: https://dx.doi.org/10.5409/wjcp.v10.i6.137

INTRODUCTION

Urolithiasis: A public health concern

Renal, ureteral and bladder stones are present in pediatric clinics and are the end product of a multifactorial process. No age or ethnic group is protected from this clinical problem that commonly afflicts humanity[1].Urolithiasis (UL) is an uncommon cause of death or end-stage renal disease; however, it represents a significant public health problem because its recurrence is a marked characteristic and confers high morbidity. No stone removal technique can decrease this recurrence or change its morbidity, which in pediatric patients is directly related to surgical interventions, to morphofunctional alterations resulting from possible obstructions of the urinary tract, and also to its clinical manifestations. In addition, they have a high potential for complications, as the symptoms are often nonspecific[2].

Incidence and prevalence

The risk of forming a new stone increases with age in patients who have already had it. Thus, the estimated risk of forming a new stone in one year is 15%, 35-40 % in five years and 80 % in ten years[3]. Its prevalence varies according to varied factors such as ethnicity, geographical location, water consumption of that population and age group. Despite being more common in whites and men, new studies have shown that UL is becoming more common in female and black patients[4].

Data on the prevalence and incidence of urinary tract stones in childhood are still scarce in the literature. The true incidence of this disease remains unknown due to the multiplicity of etiopathogenic factors and the non-specificity of the clinical onset. Variations in this incidence are found from 1:1714 to 1:9500 cases in different regions of the United States. However, it is believed that the prevalence is 5% in white North American children[5].

Urinary stones can occur anywhere in the renal collecting system. In industrialized countries, 97% of urinary stones are found in the parenchyma, pelvis, papillae and calyxes, while only 3% in the bladder and urethra. Bladder stones are more frequent in developing countries. The formation of stones in the kidneys and urinary tract is dependent on crystals and matrix, and its constituents are, in most cases, different organic and inorganic substances with a crystalline or amorphous structure. Only one-third of urinary stones have only one mineral in its composition, with calcium oxalate being the most common and found in at least 65% of all stones[2,6].

Risk factors

Several factors are involved in urinary stones formation, such as: infectious, anatomical, epidemiological, climatic, socioeconomic, dietary, genetic and metabolic. These factors, combined with physicochemical and physiological changes in the urine, alter the elements that promote and inhibit the aggregation and growth of crystals, culminating in the formation of stones[6]. However, the etiopathogenesis of UL remains unclear, and multiple aspects still have no explanation.

Crystallization begins when the urine is supersaturated for a particular solute. If the solution is unsaturated, crystals do not form. Supersaturation depends on ionic

strength, abnormalities in urinary pH, reduced urinary volume, deficiency of crystallization inhibitors (citrate, magnesium, pyrophosphate, nephrocalcin, glycosaminoglycans) and the hyperexcretion of calcium, uric acid, phosphorus and more rarely of oxalate and cystine. However, it is not clear how the crystals formed in the tubules become calculi since they are continuously washed away by the urine flow. It is believed that these aggregated crystals reach a certain dimension that allows an anchoring process, usually at the end of the collecting ducts and, slowly, they increase in size over time. This anchoring process is likely to be induced by the crystals themselves and occurs in damaged sites of the tubular epithelial cell. Currently, new studies on the etiopathogenesis of UL and molecular biology have contributed to these new discoveries. The identification of other molecules in the urine with inhibitory capacity for crystallization, as well as the new principles of adhesion of the crystals in the renal tubular epithelium and the endocytosis suffered by the calcium oxalate crystals in the renal tubular cells, are the main examples[7,8].

Some factors are considered main risks for UL, such as excessive salt and animal protein intake, low water intake, use of lithogenic drugs, genetic inheritance and dietary calcium restriction[6]. Unlike what happens in adult patients, overweight and obesity still do not show consistent scientific evidence for pediatric patients with UL [6]. The high sodium intake in healthy people induces an increase in urinary calcium excretion. Experimental studies show that the increase in fractional excretion of sodium in the proximal tubule produces an increase in fractional excretion of calcium in this same tubule, with consequent hypercalciuria, determining a positive correlation between natriuria and calciuria. A high amount of salt in the diet also determines a reduction in citrate excretion by mechanisms not yet known[9,10].

Penido *et al*[11] demonstrated that healthy children and adolescents ingested a higher amount of sodium and proteins and lower amounts of calcium than recommended by the RDA, in all age groups, in a Brazilian pediatric cohort. The authors also found a positive correlation between urinary sodium and calcium excretion ($r = 0.74$; $P < 0.01$)[11]. The high animal protein intake increases the production of fixed acids, causing transient metabolic acidosis. Consequently, there is an increase in urinary calcium excretion, accompanied by urinary pH reduction, hyperexcretion of uric acid, oxalate, and hypoexcretion of citrate, predisposing to UL[6,11].

Oliguria is also a significant risk factor for stone formation. Maintaining adequate urine volume is essential to ensure the solubility of substances excreted in the urine. The reduced urine output is a consequence of decreased water intake, which increases the saturation of solutes and predisposes to the formation of urinary calculi. Studies have shown that calcium oxalate supersaturation increased significantly once urine output decreased to less than 1.0 mL/kg per hour[6,12].

Drugs that promote crystalluria such as sulfadiazine, triamterene, indinavir and ceftriaxone favor the formation of calculi. Inappropriate use of antibiotics is also related to the formation of urinary stones[13]. Oxalate is degraded by Oxalobacter formigenes, Bifidobacterium, Lactobacillus, Escherichia coli, and others that reduce its intestinal absorption and protect against the formation of stones. Antibiotics alter the intestinal microbiome and consequently the oxalate metabolism. Exposure to any of the five main classes of antibiotics in the 3-12 mo prior to calculi formation was associated with an increased risk of stones (sulfas, cephalosporins, fluoroquinolones, nitrofurantoin and penicillin). The magnitude of this association was higher for exposure at younger ages and 3-6 mo before the diagnosis of UL[13].

Mode of Inheritance

Individuals with a positive family history of UL have a relative risk of developing urinary stones 2.57 times greater after an eight-year period when compared to those without. Cystinuria and primary hyperoxaluria are monogenic diseases whose mutations were already described. However, it is in IH that this genetic involvement has been widely studied, and 40% of patients with this disease have a family history of UL. Experimental models have suggested a possible dominant inheritance for IH. Polymorphism of vitamin D receptor genes has also been linked to urinary calcium excretion. It seems to represent one of the genetic factors that affect bone mineral density, although it only partially contributes to the genetic effect on bone mass, and this is not observed in all evaluated populations[14,15].

Metabolic disturbances

Important calcium restriction in the diet determines an increase in urinary oxalate excretion and, consequently, an increased risk for the aggregation of calcium oxalate crystals. In addition, they can facilitate the occurrence of reduced bone mineral density (BMD)[22]. Metabolic alterations are responsible for 80% to 90% of stone formation in

adults as well as in childhood. The most common alterations in pediatric patients are hypercalciuria, hypocitraturia, and low urine output[2,6,16]. As aforementioned, the IH is the leading metabolic risk factor for UL, and it has become more common in children over the past few decades. It has high morbidity with or without UL, and reduced BMD was already described in pediatric patients[16].

HYPERCALCIURIA

In 1953 Albright *et al*[17] used the term "idiopathic hypercalciuria" for the first time. In 1962, Valverde published his firsts Spanish pediatric cases[18]. In the same year, two pediatric groups reported six cases of children with hypercalciuria, osteopenia or rickets, nanism and renal impairment. The authors proposed that those cases would be IH; however, the patients were probably carriers of other tubulopathies[19]. After this publication, others emerged discussing the definition of criteria regarding "primary/idiopathic hypercalciuria" (see below).

IH is a metabolic disorder that affects all ages, genders and race groups[2,20,21]. It has a high prevalence and is the major risk factor to UL in children[2,20] and adults [22]. The "true" IH is a clinical condition characterized by increased urinary calcium excretion in the absence of hypercalcemia or other clinical conditions that can cause hypercalciuria and when dietetic disturbances have been excluded[23-25]. Its incidence in the pediatric group range between 2.2%-6.2%[25] and the prevalence between 0.6% and 12.5%. In Spain, prevalence rates vary between 3.8% and 7.8%[23].

Hypercalciuria is defined as urinary calcium excretion higher than or equal to 4 mg/kg/d for any gender or age[11,26]. Another clinical definition is the random or spot urinary calcium/creatinine ratio. It could be especially useful for children who do not have urinary sphincter control (Table 1)[11,26]. It is important to highlight that young children and infants have higher urinary calcium excretion and lower urinary creatinine levels. Then, the calcium/creatinine ratios differ by age (Table 1)[11,26]. Normal values for the lithogenic substances are described in Table 1.

IH can be related to two conditions: UL and bone resorption. Studies have demonstrated that hypercalciuric calcium stone formers have decreased BMD when compared to matched controls which are neither stone formers nor hypercalciuric[27,28]. Among adults patients with UL, those with hypercalciuria will have BMD measurements 5% to 15% lower than their normocalciuric matched controls[27]. Several studies have also demonstrated reductions in BMD in hypercalciuric pediatric patients with or without hematuria or UL[16,29-34]. This review discusses the association between UL, IH and reduced BMD in pediatric patients and the importance of this association for the clinical practice of pediatricians.

PATHOGENESIS OF HYPERCALCIURIA

The pathogenesis of IH is complex and not yet completely understood. We would say that the excretion of calcium in urine is the end result of an interplay between three organs: the kidneys, bones and gastrointestinal tract. These organs are orchestrated by hormones, such as parathyroid hormone (PTH), calcitonin, 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2$D3), fibroblast growth factor (FGF23), and probably others unknown, acting together as a unique system. It seems that IH is a systemic abnormality with alterations in calcium cellular transport in kidneys, bones and intestines (Figure 1)[22,35,36].

In 1965, Edwards & Hodgkinson started the first studies on the pathogenesis of IH and concluded that its origin should be exclusively renal[37]. Chronic loss of calcium by the kidneys would lead to a reduction in serum calcium, and consequently, an increase in serum PTH. Considering this, Pak *et al*[38] in 1974 observed normal levels of PTH in their hypercalciuric patients and ruled out the possibility that IH was exclusively of renal origin. The same authors proposed a test (acute oral calcium overload test) to distinguish two types of IH, according to the underlying pathophysiological mechanism: absorptive or renal. They classified IH into three distinct pathogenetic pathways: (1) Absorptive hypercalciuria type I (primary intestinal hyperabsorption of calcium); (2) Absorptive hypercalciuria type III (primary renal leak of phosphate); and (3) Renal hypercalciuria (primary renal leak of calcium)[39]. These authors also identified the so-called resorptive hypercalciuria when hypercalciuria is induced by an excessive calcium output from bones. However, the clinical value of the classification was limited, and it is often impossible to classify the patient into a

Table 1 Normal values for random urine and 24 h urine factors for children and adolescents

	24 h urine	Random urine corrected by creatinine		Random urine factored for GFR
Volume	≥ 1.0 mL/kg per h			
Creatinina	2 to 3 yr: 6 to 22 mg/kg; > 3 yr: 12 to 30 mg/kg			
Calcium	< 4.0 mg/kg (0.10 mmol/kg)	Age	mg/mg; mmol/mmol	< 0.10
		0-6 mo	< 0.80; < 2.24	
		6-10 mo	< 0.60; < 1.68	
		1-2 yr	< 0.40; < 1.12	
		2-18 yr	< 0.21; < 0.56	
Citrate	≥ 400 mg/g creatinine	≥ 0.28 (mmol/L/mmol/L)		> 0.18 (mg/L/mg/L)
Calcium/Citrate	< 0.33	< 0.33		
Na/K	< 3.5	< 3.5		
Uric acid	< 815 mg/1.73m^2 BS	< 0.65		< 0.56 mg; < 0.03 mmol
Cystine	< 60 mg/1.73 m^2 BS	< 0.02 (mg/mg); < 0.01 (mmol/mmol)		
Magnesium	> 88 mg/1.73 m^2 BS			
Phosphate	TP/GFR[1]: > 2.8 and < 4.4 mg/dL			
Oxalate	< 50 mg/1.73m^2 BS; < 0.49 mmol/1.73m^2 BS	Age	(mg/mg)	
		0-6 mo	< 0.30	
		7 mo - 4 yr	< 0.15	
		> 4 yr	< 0.10	

[1]TP/GFR = Pp – (Pu × Crp)/Cru.

GFR: Glomerular filtration rate; TP: Tubular phosphate reabsorption; Pp: Plasma phosphate; Pu: Urinary phosphate; Crp: Plasma creatinine; Cru: Urinary creatinine. Adapted from: Penido MGMG, Tavares MS. Pediatric primary urolithiasis: Symptoms, medical management and prevention strategies. *World J Nephrol* 2015; **4**: 444-454. Copyright ©The Author(s) 2015. Published by Baishideng Publishing Group Inc[2].

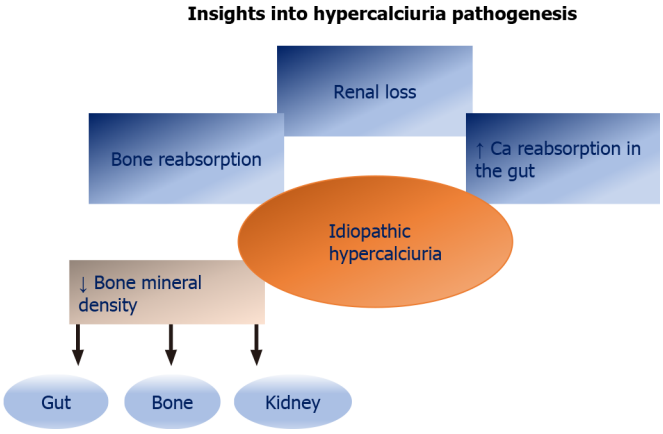

Figure 1 Insights into hypercalciuria pathogenesis (Source: Nephrology Center of Santa Casa de Belo Horizonte - Pediatric Nephrology Unit - by Penido MGMG).

specific type, as described by Aladjem *et al*[40] (1996) in children. Thus, this test and this classification fell out of use.

Alhava *et al*[41] demonstrated that their patients with UL had significantly lower BMD values when compared to controls. In the 1980s, with the assessment of 1,25OH vit. D, it was proven that some of these patients with urinary stones had high levels of this vitamin[42]. The hypothesis of intestinal IH was again highlighted. Buck *et al*[43]

treated 43 patients with HI and hyperproduction of prostaglandin E2 (PGE2) with indomethacin. The authors confirmed the normalization of the calciuria and suggested that PGE2 could be implicated in the origin of IH[43]. Henriquez-La Roche *et al*[44] have also shown an increase in PGE2 in patients with IH.

Urinary phosphate loss was related to IH, and when hyperphosphaturia is important, it favors hypophosphatemia. The reduction in serum phosphate levels favors calcitriol synthesis, increasing intestinal calcium absorption and, consequently, hypercalciuria. A study by Prié and co-workers showed that 20% of hypercalciuric stone-formers with normal PTH have a decreased TmP/GFR (tubular phosphate reabsorption / glomerular filtration rate) value and phosphaturia[45].

Pacifici *et al*[46] demonstrated that blood monocytes from patients with IH produced an increased amount of cytokines: interleukin-1 (IL-1), granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor (TNF-alpha). The increased activity of these cytokines had the ability to reduce BMD in patients with IH, and other studies confirmed these findings[47,48].

Weisinger[49] proposed a new theory on the pathophysiology of HI that combined the findings already published: IL-1 and the other cytokines would stimulate bone resorption[46-48] and the production of PGE2 [44]that induced the synthesis of calcitriol[50]. It is known that an excessive amount of calcitriol stimulates bone resorption[50]. Thus, hypercalciuria would be caused by an increase in bone resorption and an increase in intestinal calcium absorption due to the effect of calcitriol.

Inflammatory mediators such as IL-1 and TNF reduce the epithelial sodium transport due to increased PGE2 synthesis[51] and reduced expression of the epithelial sodium channel (ENaC) and/or Na + -K + -ATPase in the basolateral membrane[52]. A slight distal saline loss has been described in some adult patients, and this loss of sodium would increase urinary calcium[53]. These patients could have a triple origin for IH: bones, intestines and kidneys.

Rats with spontaneous hypercalciuria (genetic hypercalciuric stone-forming - GHS) were identified, and an increase in calciuria was observed in each successive generation of them[54]. Bushinsky and Favus observed that these rats had excessive calciuria due to an increase in the intestinal absorption of this ion, although calcitriol levels were normal[54]. When the rats were submitted to a calcium-restricted diet, the calciuria decreased, suggesting that the mechanism of hypercalciuria observed in these animals was the increase in intestinal calcium absorption[55]. A higher number of vitamin D receptors (VDR) in the intestine of these rats was demonstrated, favoring the functional capacity of calcitriol-VDR complexes[55]. Yao *et al*[56] found that these animals had an increased response to VDR with minimal calcitriol levels, thus causing hypercalciuria. However, this loss of calcium was greater than dietary intake, suggesting another pathogenic mechanism. In sequence, Krieger *et al*[57] demonstrated that this increase in sensitivity to calcitriol was expressed in the bones of these animals, inducing bone resorption, leading to a possible role of bones. Later, Tsuruoka *et al*[58] demonstrated that hypercalciuric rats have a tubular calcium reabsorption defect. This is due to an activation of the sensitive calcium receptor (CaR) that would suppress the activity of the calcium-sensitive potassium channel (ROMK) in ascending portion of the loop of Henle[59]. There is a reduction in the electrical gradient in the tubular lumen with a consequent reduction in the absorption of calcium by the paracellular pathway. Consequently, more calcium is delivered to the distal tubule. In humans, Worcester *et al*[60] showed that hypercalciuric stone-forming patients, eating fixed and identical high-calcium and regular diets, reduce distal and proximal tubule reabsorption more than controls. Favus *et al*[61] demonstrated that peripheral monocytes of humans with IH have an increased VDR number, as previously described in hypercalciuric rats[55]. Based on suggestions by Worcester and Coe[22] that variations in the klotho-FGF23 axis could mediate alterations in calcium and phosphate handling by the kidney and play a role in IH, Penido *et al*[62] decided to explore a potential role for FGF23 in pediatric IH. They concluded there was no difference in plasma FGF23 Levels between hypercalciuric and control children[62]. Pharmacologically treated patients had significantly lower urine calcium excretion rate and plasma FGF23 Levels; elevated TP/GFR and serum phosphate without changes in serum PTH values. It thus seems that the reversal of hypercalciuria may directly or indirectly affect phosphate metabolism[62]. Finally, what has been demonstrated in hypercalciuric rats has also been found in humans with IH: increased intestinal calcium absorption, defect in tubular calcium reabsorption, increased bone resorption, and normal serum calcium and calcitriol levels[61].

The excess sodium intake is accompanied by increased urinary calcium excretion and increased dietary protein intake[63,64]. Breslau *et al*[65] suggested that hypercalciuria induced by excess dietary sodium was accompanied by an increase in calcitriol

synthesis. Excessive protein intake produces acid overload that inhibits renal tubular calcium reabsorption. The increase in net acid production is buffered by bones and other body buffers[63,65]. It could explain the reduction in BMD in IH. Bataille *et al*[66] observed a direct correlation between calciuria and urinary hydroxyproline in their patients, a marker of bone resorption.

The genetic background is also involved in the pathogenesis of IH. It has been described that patients with UL due to hypercalciuria can be carriers of genetic polymorphisms that encode certain proteins involved in the tubular reabsorption of calcium and phosphate (VDR, SLC34A1, SLC34A4, CLDN14, CaSR, TRPV6), or in the prevention of it precipitation of calcium salts (CaSR, MGP, OPN, PLAU, UMOD)[67-69]. Garcia Nieto *et al*[23] published a summary with all the pathophysiological mechanisms involved in IH described to date (Figure 1). According to the authors, it remains to be determined whether the cytokine-producing monocyte hyperreactivity described in IH is related to the increase in VDR in these cells (Figure 2).

Another point to discuss is the role of vitamin D supplementation. This supplementation has been related to hypercalciuria. Milart *et al*[69] analyzed the impact of vitamin D supplementation on 36 children with IH and UL prospectively. Blood and urine samples were collected every three months up to 24 mo of vitamin D intake at a dose of 400 or 800 IU/d. Bone densitometry was performed at time 0, at 12, and 24 mo of vitamin D supplementation. The authors concluded that supplementation with vitamin D caused an increase in 25(OH) vit. D in serum[69]. However, no changes in serum calcium, urine calcium and bone density were observed. There was no significant increase in the risk of development of kidney stones[69].

CLINICAL PRESENTATION OF HYPERCALCIURIA IN PEDIATRICS

Pediatricians are professionals who assist children and adolescents with UL and IH. It is imperative that these professionals have knowledge about these clinical entities and how they present in pediatric patients. IH in children can present as gross or microscopic hematuria, voiding symptoms (urinary urgency, pollakiuria, dysuria, incontinence, enuresis and suprapubic pain), recurrent abdominal pain and flank pain in the absence of calculi, lumbar colic, urinary tract infections or enuresis and other voiding disorders[21,70,71]. Macro or microscopic hematuria and/or abdominal pain are the most common clinical presentations among hypercalciuric pediatric patients [21,25]. Unlike adults, lumbar colic is not common in children, and Penido *et al*[21] found only 14% of lumbar colic as first presentation. These different signs and symptoms can be confusing at the time of clinical presentation. Pediatricians should be aware of this diagnosis in children and adolescents who present clinically with urinary urgency and incontinence, suprapubic pain, nocturnal enuresis, pain in the urethra and recurrent chronic abdominal pain. In this sense, IH must be identified and monitored because it can have consequences other than hematuria, abdominal pain and kidney stones.

BONE CHANGES IN HYPERCALCIURIA

Reduced BMD has been described in adult patients with IH since the 1970s[41,47,48,66], and since then, it has been recognized that hypercalciuric patients with UL could exhibit a decrease in BMD. Different factors may be involved in bone loss in IH, such as negative calcium balance due to reduced tubular reabsorption, increased production of prostaglandin E2[44], increased cytokine reabsorption activity[46] and/or calcitriol[72]. An increased resorptive action of calcitriol would be related to an increased number of VDR[57].

Bone biopsies performed in a patient with IH showed an increase in osteoclastic activity[73], and in some series, a reduction in osteoblastic activity was observed[74]. Gomes *et al*[74] demonstrated a high expression of the receptor activator of nuclear factor kappaB ligand (RANKL) in patients with IH, suggesting an increase in bone resorption mediated by this peptide. The authors found that expression of IL-1 and basic fibroblast growth factor (bFGF) was similar to that of controls and consider that the high expression of cytokines, already described in hypercalciuric patients, could have no causal relationship with the reduction in bone mass. Therefore, Gomes *et al* [74] considered that the primary event would be the increase in VDRs, which favors the increase of the functional capacity of calcitriol-VDR complexes, increasing intestinal calcium absorption, and stimulating the bone expression of RANKL.

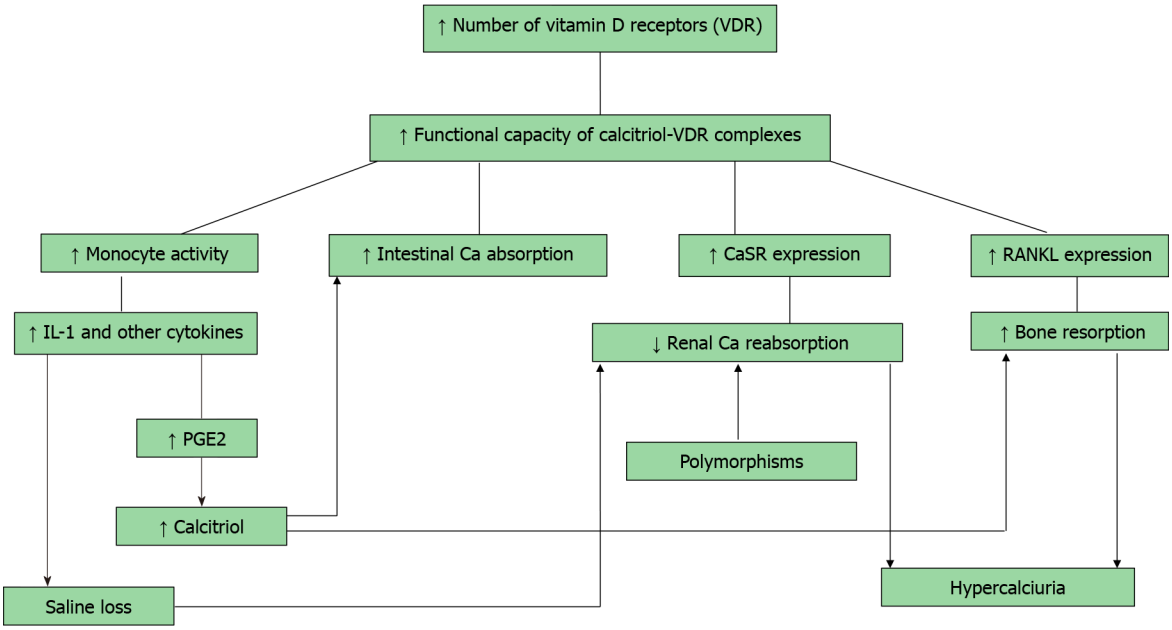

Figure 2 Cytokine-producing monocyte hyperreactivity described in IH is related to the increase in VDR in these cells. Adapted from: García-Nieto VM, Luis-Yanes MI, Tejera-Carreño P, Pérez-Suarez G, Moraleda-Mesa T. The idiopathic hypercalciuria reviewed: Metabolic abnormality or disease? *Nefrologia* 2019; 39: 592-602. Copyright ©The Author(s) 2019. Published by Elsevier España, S.L.U[23].

In 2020, Taguchi *et al*[75] performed a single-center retrospective cohort study to analyze patients with UL who underwent both BMD examination and 24 h urine collection. A total of 370 patients were included, and there was a positive correlation between BMD T-scores and urinary phosphate and citrate excretion. A lower BMD T-score was associated with increased odds ratios for stone symptoms during follow-up. The authors suggested that examining BMD could be a useful tool for effective follow-up of UL and may prevent future risks factors to urinary stones[75].

BONE CHANGES IN PEDIATRIC HYPERCALCIURIA

It is known that life-long hypercalciuria could be an important contributor to diminished bone mass or failure of adequate bone mass gain. In pediatric patients, the studies on IH began with Stapleton *et al*[20,76,77]. The authors used the acute oral calcium overload and found similar linear skeleton growth in both groups (renal and absorptive hypercalciuria)[77]. The same authors studied the BMD of their patients with IH and compared it with a control group. They found no significant differences in BMD between patients and controls or between patients with renal and absorptive hypercalciuria. Also, there was no correlation between BMD, PTH and osteocalcin[77]. Later, studies showed bone changes in pediatric patients with IH. Perrone *et al*[78] showed an improvement in lumbar spine BMD (compared to those untreated) in a prospective study with pediatric IH patients with absorptive type treated with dietary calcium restriction and/or rice bran The BMD of the lumbar spine (L2-L4) and bone markers of bone formation and resorption were assessed in children with IH[78]. The patients had elevated osteocalcin and calcitriol blood levels, as well as magnesium and prostaglandin E2 urinary levels. On the other hand, they had decreased urinary ammonium excretion, tubular reabsorption of phosphate and BMD when compared to controls[78]. BMD reduction was present in 30% of the patients and was negatively correlated with age. The authors hypothesized the increased cytokine activity could explain the reduced BMD in these patients[79]. Freundlich *et al*[31] studied the BMD (lumbar spine and femur) and bone resorption markers (pyridinoline, deoxypyridinoline and telopeptide) of children with IH and of their premenopausal mothers. The authors found BMD reduction in 38% of children and 33% of their mothers. The bone resorption markers were increased in 57% of the mothers with BMD reduction [31]. Garcia Nieto *et al*[29] described the BMD *Z* score as < -1 in 30.1% of their pediatric patients with evaluated IH. Bone markers were analyzed to confirm the resorptive mechanism in pediatric patients with HI. In children with normal BMD, a direct correlation was observed with the levels of osteocalcin (bone formation marker) and

tartrate-resistant acid phosphatase, a bone resorption marker; however, this relationship disappeared in those with reduced BMD[29]. Subsequently, the authors verified a value of < -1 for BMD *Z* score in the lumbar spine in 42.5% of a group of girls and in 47.5% of their mothers (lumbar spine and/or femoral neck). Mothers and daughters had hypercalciuria[32]. More sensitive resorption markers such as deoxypyridinoline (DPir) and the C-terminal telopeptide collagen fraction in the urine (CTx) were evaluated. Hypercalciuric children with or without BMD reduction showed significantly higher values of DPir/Creatinine and CTx/Creatinine ratios than controls. In contrast, osteocalcin levels were significantly higher only in patients with normal BMD[32]. These data would confirm that there is an increase in osteoclastic activity in children with IH, and those with normal BMD would have an adequate compensatory osteoblastic response[23].

Penido *et al*[16] evaluated a group of 88 children with IH at the time of diagnosis and 29 controls. BMD *Z*-score was significantly reduced at the lumbar spine in 31 (35%) patients. The biochemical markers of bone turnover were also evaluated. There was an increased urinary N-telopeptide excretion in the hypercalciuric subjects, as well as increased serum osteocalcin. The authors suggested that the low bone mass in children with IH might have been due to increased bone turnover[16].

Skalova *et al*[33] evaluated 15 pediatric hypercalciuric patients, and 40% of them had BMD Z-scores between -1 and -2 standard deviations (SD), and 20% had BMD Z scores below -2 SDs. The values for 24 h urinary calcium and N-acetyl-β-D-glucosaminidase (NAG - marker of renal tubule impairment) were significantly higher, and lumbar BMD was significantly lower than reference values from a healthy European pediatric population. The authors also demonstrated an inverse correlation between BMD and 24h calciuria[33].

Later, Penido *et al*[80] evaluating 88 pediatric patients with IH, and half of them had associated hypocitraturia (HC). Those with HC had a higher reduction in BMD in the absence of metabolic acidosis. A significant reduction in blood pH and bicarbonate in the group with HC was observed, although venous blood gases were normal in all patients. The authors suggested that lower blood pH and bicarbonate in hypercalciuric patients with associated HC could indicate that there is an intracellular acidification defect more severe in those patients with HC. This acidic environment would stimulate bone buffering, hypercalciuria and reduced BMD. Although age did not differ between patients with and without HC, those with HC had significantly lower height, weight, bone age and body mass index (BMI), suggesting an effect of HC on growth[80].

In 2009, Garcia Nieto *et al*[23] evaluated the BMD of 104 children with IH on two occasions. The first bone densitometry was performed at 10.7 ± 2.6 years and the second at 14.4 ± 2.7 years[34]. There were no differences in the calciuria or citraturia values or age at the time of the two bone densitometries. The authors concluded that there is a tendency to improve BMD in children with IH spontaneously, which is associated with increased body mass[34].

Penido *et al*[30] studied the BMD at the lumbar spine of 80 pediatric patients with IH. BMD Z-scores were evaluated before and after treatment. The patients were followed for a median time of 6.0 years, and they were treated with potassium citrate or potassium citrate and thiazides. BMD Z-score changed significantly from -0.763 ± 0.954 to -0.537 ± 0.898 ($P < 0.0001$). The authors suggested a beneficial effect of treatment in these patients, with significant improvement in bone mass[30].

Pavlou *et al*[81] in 2018 investigated 50 children with IH and matched 50 controls in a prospective study. They evaluated biochemical markers of bone formation and resorption and the osteoprotegerin (OPG) and soluble receptor activator of the nuclear factor-kB ligand (sRANKL) system. Following the diagnosis, the patients were requested to follow a 3 mo dietary recommendation. At diagnosis and at 3 mo of follow-up, patients and in controls were studied for bone-related hormones and serum/urine biochemical parameters. The authors concluded that children with IH had biochemical markers compatible with normal bone formation but increased bone resorption. After a 3 mo dietary intervention, the decrease in the serum β-Crosslaps may have reflected a beneficial response[81].

Kusumi *et al*[82] in 2020 conducted a prospective paired case-control study to assess BMD in adolescents with UL and to evaluate a possible correlation between BMD and urine concentration of lithogenic minerals and/or inflammation markers. It was observed that the BMD Z-score of lumbar spine and total body were not different between groups; however, when patients were separated by gender, there was a significant difference between males *vs* controls for the BMD Z-score of total body. There was no correlation of the lumbar spine and total body BMD Z-score regarding urinary calcium, oxalate, citrate or magnesium. Higher urine IL-13 significantly

correlated with higher total body BMD Z-score (r = 0.677; P = 0.018). The authors concluded that despite the small number of patients, it is a hypothesis-generating study. They demonstrated novel evidence of male-specific low BMD in adolescent stone formers[82].

Recently, Perez-Suarez *et al*[83] (2021) evaluated 34 hypercalciuric pediatric patients in a longitudinal study conducted over 20 years through three bone densitometry studies. Patients underwent a third densitometry study in adulthood (10.5 ± 2.7 [BMD1], 14.5 ± 2.7 [BMD2] and [BMD3] 28.3 ± 2.9 years of age). The authors observed a gradual decrease in calcium/creatinine and citrate/creatinine ratios and suggested that it would be related to improvement in osteoblastic activity and especially reduction in osteoclastic activity. They concluded that in patients with IH, BMD improves with time. This improvement may be related especially to the female gender, increment of body mass, and reduction in bone resorption. Urine calcium and citrate excretion tend to decrease upon the patients reaching adulthood[83].

At this point, it is known that IH and reduced BMD are closed entities. However, the precise mechanisms of reduction in bone mass loss or failure of normal bone mass gain remain not entirely known.

IMPORTANCE OF HYPERCALCIURIA FOR PEDIATRICIANS

The peak bone mass and its accumulation are achieved by late adolescence, peaking at the end of the second decade of life[84]. This accumulation should occur without interference in order to achieve the peak of optimal bone mass. The bone mass acquired during childhood and adolescence is a major determinant of adult bone health, and its accumulation should occur without interference[85]. This raises the important question of whether adult osteoporosis is initiated during childhood in IH patients[84]. However, interferences in childhood bone mass acquisition would not affect bone mass in late adulthood because there is a homeostatic system that seeks to return to the normal situation after any transient change[85].

Studies have emphasized that a persistent disturbing factor would, therefore, compromise the final bone mass in adulthood[85]. According to these studies, "any continuous and persistent interference may be a determining factor for low BMD with increased risk of osteopenia, osteoporosis and fractures in adulthood"[85].

An important point is how to assess and interpret BMD in children. According to the ISCD official position, DXA is the preferred method. Bone mineral content (BMC) and areal BMD results should be adjusted for absolute height or height age or to pediatric reference data that provide specific *Z* scores. The terms osteopenia and osteoporosis should not be used in pediatric patients. The correct term for them is "low bone mineral content" or "low bone mineral density" for age, when the *Z* scores are less or equal minus two[86].

There are few studies showing the association between decreased BMD and fractures in children. Data suggest that children with abnormal BMD are at risk for fractures. However, none of those included a biochemical analysis to assess other potential causes of low BMD[87,88]. In a case-control study, Olney *et al*[88] showed that BMD values were lower for the case subjects with fractures compared with the control subjects. The authors decided to evaluate these patients because both pediatricians and orthopedists are often unsure whether to consider further evaluation in children with repeat fractures[88].

CONCLUSION

Considering all the aforementioned, it is imperative that pediatricians have the knowledge and ability to diagnose and manage pediatric patients with IH with or without UL. They should advise parents and/or caregivers that children and adolescents must always have a healthy diet with a regular intake of calcium, proteins, calories and sodium, according to RDA; practice daily physical exercises; adequate fluid intake, especially water as well as regular sun exposure. If regular sun exposure is not possible, the serum levels of 25OH Vit. D should be assessed. The control of risk factors and adequate treatment (pharmacological or not) are essential for great bone structure and bone mass throughout life, decreasing the risk of osteopenia, osteoporosis and fractures later in life.

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World Journal of Clinical Pediatrics

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World J Clin Pediatr 2021 November 9; 10(6): 151-158

DOI: 10.5409/wjcp.v10.i6.151

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Retrospective Study

Pediatric firearm-associated fractures: Analysis of management and outcomes

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Author contributions: Swarup I designed the research and supervised and contributed to the report; Pandya NK supervised and contributed to the report; Lieu V and Carrillo LA collected and analyzed the data and wrote the paper.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Board at UCSF Benioff Children's Hospital Oakland.

Informed consent statement: The informed consent statement was waived by the Institutional Review Board.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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Abstract

BACKGROUND

Firearm-associated injuries (FAIs) are among the leading causes of morbidity and mortality in children living in the United States. Most victims of such injuries survive, but may experience compromised function related to musculoskeletal injuries. Although complex firearm-associated fractures (FAFs) often require specialized orthopaedic, vascular, and plastic surgical intervention, there is minimal research describing their management and outcomes. The purpose of this study is to describe the epidemiology and presentation of pediatric FAFs, as well as evaluate the management and outcomes of these injuries.

AIM

To describe the epidemiology and presentation of pediatric FAFs, as well as evaluate the management and outcomes of these injuries.

METHODS

A retrospective chart review was performed at a major, pediatric level 1 trauma center. The study included patients aged 18 or younger who presented with FAIs between 2008-2018. Additional data was collected on patients with FAFs including demographic and clinical data such as age, sex, race, payor type, fracture location, injury severity score (ISS), and radiographic and clinical outcomes. The management of FAFs was analyzed as well as need for readmission and reoperation. Descriptive statistics were used to summarize the results and univariate analyses were performed to assess differences between groups.

RESULTS

Specialty type: Orthopedics

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 7, 2021
Peer-review started: January 7, 2021
First decision: May 6, 2021
Revised: June 7, 2021
Accepted: September 22, 2021
Article in press: September 22, 2021
Published online: November 9, 2021

P-Reviewer: Mayr J
S-Editor: Zhang H
L-Editor: A
P-Editor: Yuan YY

Between 2008 and 2018, there were a total of 61 patients who presented with FAIs. In this cohort, 21 patients (34%) sustained FAFs (25 fractures) with a mean age of 11 (Range: 10 mo to 18 years old) at the time of presentation. Approximately 52% (n = 11) of patients with FAFs were male, 76% (n = 8 and n = 8, respectively) identified as black or other, and 71% (n = 15) had government insurance. FAFs were most commonly noted in the upper extremity (n = 7) and lower extremity (n = 6). In patients with FAFs, the mean ISS at presentation was 11.38 (Range: 2-38), and 24% of patients (n = 5) were classified as having a major trauma. There were no significant differences in age, sex, race, and payor type in FAF patients that presented with and without major trauma (P > 0.05). When comparing FAF and non-FAF patients, there was a statistically significant difference in ISS (11.38 *vs* 14.45, P = 0.02). In total, 33% (n = 7) of patients with FAFs required orthopaedic surgical management, which was most commonly comprised of debridement (n = 6/7, 86%), and 14% (n = 1/7) of these patients required coordinated care with plastic and/or vascular surgery. There were no significant differences in age and payor type in patients with FAFs treated with and without orthopaedic surgery. Of the patients with FAFs, 52% (n = 11) had a minimum 90-d follow-up, and 48% (n = 10) had a minimum 2-year follow-up. Two patients were readmitted within 90-d, while one patient required a reoperation within 2-years.

CONCLUSION

Over 25% of FAIs in pediatric patients result in FAFs. FAFs often present to pediatric trauma centers and the majority of these injuries occur in non-Caucasian males with government insurance. Most FAFs do not need orthopaedic surgical management; 14% of these injuries require subspecialty care by orthopaedic surgery, vascular surgery, or plastic surgery. Patients with FAFs also have lower ISS compared to patients who sustained FAIs without fracture. Thus, these patients should be treated at pediatric trauma centers with specialty care and additional research is needed to focus prevention efforts, understand reasons for poor follow-up, and evaluate outcomes after injury.

Key Words: Firearm; Fracture; Adolescent; Gunshot; Injury; Pediatric

Core Tip: Over 25% of firearm-associated injuries (FAIs) in pediatric patients result in firearm-associated fractures (FAFs). FAFs often present to pediatric trauma centers and the majority of these injuries occur in non-Caucasian males with government insurance. Most FAFs do not need orthopaedic surgical management; 14% of these injuries require subspecialty care by orthopaedic, vascular, or plastic surgery. Patients with FAFs have a lower injury severity score compared to patients who sustained FAIs without fracture. These patients should be treated at pediatric trauma centers with specialty care. Additional research is needed to focus prevention efforts, understand reasons for poor follow-up, and evaluate outcomes after injury.

Citation: Lieu V, Carrillo LA, Pandya NK, Swarup I. Pediatric firearm-associated fractures: Analysis of management and outcomes. *World J Clin Pediatr* 2021; 10(6): 151-158
URL: https://www.wjgnet.com/2219-2808/full/v10/i6/151.htm
DOI: https://dx.doi.org/10.5409/wjcp.v10.i6.151

INTRODUCTION

Firearm-associated injuries (FAIs) are among the leading causes of morbidity and mortality in children living in the United States. Recently, the injuries and fatalities associated with firearms have come to the forefront of public discourse in the United States. These injuries account for almost twenty pediatric hospitalizations per day across the country[1], and represent the cause of death for a quarter of adolescents 15-19 years old[2].

Despite the large number of children affected by firearm-related violence, there is a paucity of literature focusing on the rates of firearm associated fractures (FAFs) as well as the orthopaedic management of these injuries. Additionally, there are few studies focusing on concomitant injuries that occur with FAFs, such as vascular and soft tissue injuries. In a study by Blumberg *et al*[3], the incidence of FAFs in patients < 20 years of age between 2003 to 2012 was 90.7 per 100000 admissions. These patients were more likely to be male, African American, and older in age. The authors also noted an increase in overall incidence of FAFs during the study period, with the largest increase in children ages 0-4. These findings underscore the need for additional research focusing on the epidemiology, management, and outcomes of FAFs so that health care professionals are better able to counsel and manage patients, as well as inform policy makers to allocate resources and focus on prevention programs.

The aim of this study was to describe the epidemiology and presentation of fractures secondary to firearm injuries among children and adolescents at a major metropolitan trauma center over a ten-year period. In addition, we aimed to assess the management and outcomes of these complex musculoskeletal injuries. We hypothesized that these injuries would be rare, and the majority of patients would not require orthopaedic surgical intervention.

MATERIALS AND METHODS

A retrospective chart review was performed at a major pediatric level 1 trauma center. This study included patients aged 18 or younger that presented with a FAI between 2008 and 2018. Additional data was collected on patients specifically presenting with a FAF. Patients with isolated fractures of the hand, spine, skull, face, or ribs were excluded. This study was approved by our institutional review board.

Patients were identified from an institutional trauma database, which provided initial demographic and clinical data. This database captures all patients with FAIs seen in the emergency room. Charts for patients with FAFs were reviewed to collect additional clinical and radiographic data. Demographic data included patient age, sex, race, and payor status. Clinical data included year of presentation, fracture location, injury severity score (ISS), surgical management, need for other surgical services, rates of 90-d and 2-year follow-up, as well as 90-d and 2-year radiographic and clinical outcomes. The data were summarized using counts, percentages, ranges, and means. Univariate analyses comprised of student's t-test and chi-square analysis were performed to compare differences in patients with and without FAFs, with and without other major trauma, and patients that were or were not treated with orthopaedic surgery. All data was stored in a password protected file and analyses were performed in Microsoft Excel (v2016.).

RESULTS

Demographics

During the ten-year study period, we identified a total of 61 patients who sustained FAIs (Figure 1). Of these, 21 patients (34%) suffered FAFs and presented for care at our institution. The average age at time of presentation for all FAIs was 11 years, and approximately 70% of patients (n = 43) were male. Approximately 80% of patients identified as black or other (n = 25 and n = 24, respectively), and 59% (n = 36) had government insurance (Table 1). The mean ISS for all FAIs was 14.48 (Range: 4 to 50).

Fractures and management

There were 25 FAFs in 21 patients over the study period. Of the patients who sustained FAFs, the average age at time of presentation was 11 years, and 52% were male (n = 11). Approximately 76% identified as black or other (n = 7 and n = 9, respectively), and 67% (n = 14) had government insurance. The most common fracture locations included the upper extremity (n = 7) and lower extremity (n = 6), specifically in the scapula and femur (n = 3 and n = 3, respectively). Four patients had multiple fractures, of which two patients had both FAFs in the foot; one patient had both FAFs in the pelvis; and one patient had FAFs in the pelvis and lower extremity. The mean ISS at presentation was 11.38 (Range: 2 to 38), and 24% of patients (n = 5) were classified as having a major trauma, defined as an ISS greater than 15. There were no statistically significant differences in age, sex, race, and payor between patients with

Table 1 Demographics of patients with firearm-associated fractures

	Number
Age at injury	
0–12 years old	9 (43%)
13–18 years old	12 (57%)
Sex	
Male	11 (52%)
Female	10 (48%)
Race	
Asian	2 (10%)
Black	8 (38%)
White	2 (10%)
Other	8 (38%)
Unknown	1 (5%)
Insurance payor	
Government	15 (71%)
Non-government	6 (29%)
Location of fracture	
Upper extremity	7 (28%)
Lower extremity	6 (24%)
Foot	5 (20%)
Pelvis	5 (20%)
Unknown	2 (8%)
AO fracture classification	
14.A1	61A1.3
14A3	61A2.2
14B1	61A2.3
14B2	62A2.1
21.B1	81.1.C3
2R2C3	82.C3
31.3A3	82C1
32.C3	84B
33A3.2	87.C3
34B1.2	
42.A2	
Injury severity score	
≤ 15	16 (76%)
> 15	5 (24%)
Treatment	
Orthopaedic surgical management	7 (33%)
Debridement[1]	6 (86%)
Internal fixation[1]	5 (71%)
Both[1]	4 (57%)

No orthopaedic surgical management	10 (48%)
Unknown	4 (19%)

[1]The percentages are out of the total number of patients treated with orthopaedic surgical management.

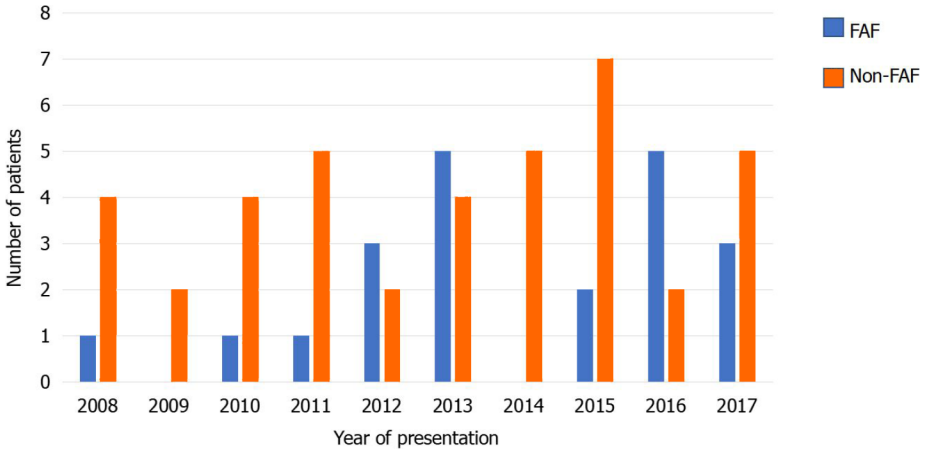

Figure 1 Number of patients with firearm-associated fractures versus non-firearm-associated fractures per year from 2008 to 2018.

and without major trauma ($P > 0.05$).

In total, 33% of patients ($n = 7$) required orthopaedic surgical management, which was most commonly comprised of debridement ($n = 6$, 86%) and internal fixation ($n = 5$, 71%). Internal fixation consisted of a variety of methods, including Kirschner wires, intramedullary devices, and plating (Table 1). Intramedullary devices were commonly used for lower extremity FAFs and k-wires or plate fixation was commonly used for upper extremity FAFs. There were no significant differences in sex and payor between patients treated with and without orthopaedic surgery.

In this cohort, approximately 14% of patients ($n = 3/21$) needed coordinated care with plastic and/or vascular surgery. Of the remaining patients, 48% of patients ($n = 10$) were treated non-operatively with modified weight-bearing, bracing, or splinting.

Follow-up and outcomes

Among all FAF patients, 52% ($n = 11$) had a minimum 90-d follow-up and 48% ($n = 10$) had a minimum 2-year follow-up. Of the 7 patients treated with orthopaedic surgery, 5 patients (71%) had 90-d follow-up, and 5 patients (71%) had two–year follow-up. All patients with radiographs at two-years had evidence of radiographic healing. In this cohort, 1 patient (14%) was readmitted within 90-d for ulnar nerve reconstruction, and 1 patient (14%) required a reoperation within 2-years for a hardware removal and a subsequent reoperation for revision fixation for malunion.

FAF and non-FAF patients

In our study, 66% patients ($n = 40$) had a FAI without an associated fracture. In this group, the average age at time of presentation was 11 years. Eighty percent ($n = 32$) of these patients were male, and 85% identified as black or other ($n = 18$ and $n = 16$, respectively). 50% of these patients had government insurance. There was no statistically significant difference in age, sex, race, and payor between our FAF and non-FAF group ($P > 0.05$). However, there was a statistically significant difference in average ISS between FAF and non-FAF patients ($P = 0.02$) with average scores of 9.5 for FAF patients and 14.5 for non-FAF patients.

DISCUSSION

The United States Center for Disease Control and Prevention estimates that 3443 fatalities and 18227 nonfatal FAIs occurred in patients below 19 years old in 2017 alone [4]. In a retrospective analysis of emergency department and ambulatory visits from the National Hospital Ambulatory Medical Care Survey, Srinivasan *et al*[5] calculated

an annual rate of FAIs of 23.9 per 100000 children between 2001 and 2010. A similar trend was noted for FAFs by Blumberg *et al*[3] with a recent increase in the number of such fractures.

Our study identified a total of 61 patients affected by FAIs over the last 10 years. Of this group, 21 patients experienced a total of 25 fractures. The majority of FAFs occurred within the last 5 years of the study period. The increasing incidence of FAFs in the last 5 years as well as the affected patient population is consistent with previous studies[3,5-10]. A previous study noted an increase in nonfatal FAFs over a 10-year period, and another study noted an overall increase in FAFs over time[3,5]. Additionally, FAFs often affect both the upper and lower extremity, with the scapula and femur being the most commonly affected anatomic location. Twenty-five percent of patients were classified as having a major trauma. In this study, there was a statistically significant difference between ISS in FAF and non-FAF patients. This may be because FAFs are commonly found in the extremities and as a result, they are not associated with major trauma since they are distal to critical organs and structures.

The majority of FAIs in this study were noted to occur in non-Caucasian males and patients with government insurance. This trend was also found in our FAF patients and is representative of our patient population. These findings are consistent with findings from a large database study, which noted FAFs were more commonly found in patients who were male, black, and uninsured in comparison to children who were being evaluated for non-firearm related complaints[5]. This pervasive trend underscores the importance of interventions targeting these demographic groups and focusing our efforts on reducing the morbidity and mortality associated with FAIs in these populations.

In general, many patients with FAFs do not need orthopaedic surgical management, but orthopaedic, vascular, or plastic surgical care may be required in up to half of all patients with FAFs. This is consistent with our hypothesis and the current literature, which supports the use of local wound care and antibiotics among low-velocity gunshot wounds with stable fracture patterns[11]. However, injuries caused by high-energy weapons or those with an unstable fracture pattern, vascular injury, or significant soft tissue defects may require formal surgical irrigation and debridement, fixation, vascular repair, or grafting, with intravenous antibiotics. In addition, a recent study by Berg *et al*[9] noted that FAFs were 1.9 times more likely to be associated with vascular and nerve injury, which may require care coordination across specialties.

In our study, approximately a third of our patients required orthopaedic surgical management, and approximately 14% of these patients needed coordinated care with plastic and/or vascular surgery. There were no significant differences in sex and payor between patients treated with and without orthopaedic surgery. Despite the lower rates of operative intervention, this finding highlights the importance of multispecialty care and a practice of having these patients managed at major trauma centers. This finding may be critical for those patients requiring orthopaedic surgical management.

This study has several limitations. This is a single center study and our sample size is small, which may affect the generalizability of our findings as well as our ability to perform analyses that are adequately powered. However, our institution serves a racially and socioeconomically diverse population, and it is the only level 1 pediatric trauma center in this geographic region. Additionally, this study only has short and long-term follow-up for approximately half of the cohort, and it has limited clinical and functional data for evaluation. This limitation may be due to the high rate of referrals to our institution, but it could also reflect the need for continued emphasis on follow-up for this patient population. Although we have a low rate of patient follow-up, readmission and reoperation were noted to occur. Thus, this finding emphasizes the need for closer follow-up to monitor for complications such as infection, malunion, and nonunion, which have been well-documented in the literature[11-13]. Lastly, we do not have any patient-reported outcome measures, which limits our ability to compare outcomes to other patients or populations.

CONCLUSION

In conclusion, FAFs are noted in approximately a third of all FAIs. FAFs have become increasingly more common at our institution, and there is a high rate of FAFs among certain demographic and socioeconomic groups. While these injuries can cause lasting effects on these patients, they may not be associated with major trauma. These findings are consistent with previous studies and should serve as a call to providers, administrators, and policy makers to investigate and propose ways to address this

issue. The findings from this study also underscore the need for multidisciplinary care and close follow-up to minimize the risk of readmission, reoperation, and poor outcomes. Patients with FAFs often have complex needs and should be treated at pediatric institutions with specialty care. Additional effort is needed to maintain follow-up and decrease the risk for readmission after this injury. The identification of factors, which may prevent follow-up in this population, could provide areas to target future interventions to ensure adequate care and optimize outcomes in these patients.

ARTICLE HIGHLIGHTS

Research background

Firearm-associated injuries (FAIs) are among the leading causes of morbidity and mortality in children living in the United States. Recently, the injuries and fatalities associated with firearms have come to the forefront of public discourse in the United States.

Research motivation

Most victims of such injuries survive, but may experience compromised function related to musculoskeletal injuries. Although complex firearm-associated fractures (FAFs) often require specialized orthopaedic, vascular, and plastic surgical intervention, there is minimal research describing their management and outcomes.

Research objectives

The purpose of this study is to describe the epidemiology and presentation of pediatric FAFs, as well as evaluate the management and outcomes of these injuries.

Research methods

A retrospective chart review was performed at a major, pediatric level 1 trauma center. The study included patients aged 18 or younger who presented with FAIs between 2008-2018. Additional data was collected on patients with FAFs including demographic and clinical data such as age, sex, race, payor type, fracture location, injury severity score (ISS), and radiographic and clinical outcomes. The management of FAFs was analyzed as well as need for readmission and reoperation. Descriptive statistics were used to summarize the results and univariate analyses were performed to assess differences between groups.

Research results

Between 2008 to 2018, there were a total of 61 patients who presented with FAIs. In this cohort, 21 patients (34%) sustained FAFs (25 fractures) with a mean age of 11 (Range: 10 mo to 18 years old) at the time of presentation. FAFs were most commonly noted in the upper extremity (n = 7) and lower extremity (n = 6). In total, 33% (n = 7) of patients with FAFs required orthopaedic surgical management, which was most commonly comprised of debridement (n = 6/7, 86%), and 14% (n = 1/7) of these patients required coordinated care with plastic and/or vascular surgery. Of the patients with FAFs, 52% (n = 11) had a minimum 90-d follow-up, and 48% (n = 10) had a minimum 2-year follow-up. Approximately 2 patients were readmitted within 90-d, while one patient required a reoperation within 2-years.

Research conclusions

Over 25% of FAIs in pediatric patients result in FAFs. FAFs often present to pediatric trauma centers and the majority of these injuries occur in non-Caucasian males with government insurance. Most FAFs do not need orthopaedic surgical management; 14% of these injuries require subspecialty care by orthopaedic surgery, vascular surgery, or plastic surgery. Patients with FAFs also have lower ISS compared to patients who sustained FAIs without fracture. Thus, these patients should be treated at pediatric trauma centers with specialty care and additional research is needed to focus prevention efforts, understand reasons for poor follow-up, and evaluate outcomes after injury.

Research perspectives

Additional effort is needed to maintain follow-up and decrease the risk for readmission after this injury. The identification of factors, which may prevent follow-up in this population, could provide areas to target future interventions to ensure adequate

care and optimize outcomes in these patients.

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2021 November 9; 10(6): 159-167

DOI: 10.5409/wjcp.v10.i6.159

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Observational Study

Healthcare staff as promoters of parental presence at anesthetic induction: Net Promoter Score survey

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Author contributions: Velayos M, contributed to the design, data collection and analysis, writing and presentation; Estefanía KF, contributed to the design and conduct of the research; Álvarez M, contributed to the writing of the article; Moratilla L and Sarmiento MC contributed to data collection; Sanabria P, Hernández F and Ló pez Santamaría MV contributed to the design and writing of the study.

Institutional review board statement: The study has been reviewed and approved by the Institutional Review Board of the Clinical Research Ethics Committee, based on the Declaration of Helsinki.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study

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Abstract

BACKGROUND

Surgical intervention is usually a traumatic event that causes stress and anxiety in the pediatric patient and the family environment. To reduce the harmful effects of presurgical anxiety, parental presence during induction of anesthesia (PPIA) is one of the more notable interventions used in medical centers. However, data on this measure are difficult to evaluate and often face resistance from healthcare staff.

AIM

To analyze the perception of the healthcare workers after the implementation of a PPIA program.

METHODS

A survey was developed and sent by email to all the healthcare staff working in the children's area of a tertiary hospital. It consisted of 14 items divided into positive aspects of PPIA and negative aspects of PPIA evaluated with the use of a Likert scale (1 to 5). The demographics of the respondents were included in the data collected. The answers to the questions were interpreted through the Net Promoter Score (NPS). The statistical analysis compared the differences in the responses to each question of the survey made by the different groups of health personnel included.

RESULTS

A total of 141 surveys were sent out, with a response rate of 69%. Of the total number of responses, 68% were from women and 32% from men. The average age

enrollment.

Conflict-of-interest statement: The authors declare that they have no conflicting interests.

Data sharing statement: Technical appendix, statistical code, and data set available from the corresponding author at mariavelayos@icloud.com. Participants gave informed consent for data sharing. Participants gave informed consent for data sharing.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Specialty type: Health care sciences and services

Country/Territory of origin: Spain

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

Received: January 10, 2021
Peer-review started: January 10, 2021
First decision: February 12, 2021
Revised: April 6, 2021
Accepted: July 15, 2021
Article in press: July 15, 2021
Published online: November 9, 2021

of the participants was 42.3 ± 10.6 years. As for the positive questions about the PPIA, 83% had an NPS > 50, and only one had a score between 0 and 50, which means that the quality of the service was rated as excellent or good by 100% of the respondents. On the other hand, 100% of the negative questions about the PPIA had a negative NPS. Responses to the question "PPIA increases patient safety" were significantly different (P = 0.037), with a lower percentage of pediatric surgeons (70%) thinking that PPIA increased patient safety, compared with anesthesiologists (90%), nursing (92%), and other medical personnel (96%).

CONCLUSION

The personnel who participated in the PPIA program at our center were in favor of implementation. There were no validated arguments to support worker resistance to the development of the PPIA.

Key Words: Parental presence; Survey; Anesthesia induction; Patient-centered care; Anxiety; Surgery

Core Tip: Surgical intervention is usually a traumatic event that causes stress and anxiety in the pediatric patient and the family environment. To reduce the harmful effects of presurgical anxiety, the parental presence during induction of anesthesia (PPIA) is one of the more notable interventions used in medical centers. However, data on this measure are difficult to evaluate and often face resistance from healthcare staff. With our work, we want to emphasize the acceptance and support of the health personnel of the application of PPIA in our center and the importance of family involvement in achieving a comprehensive approach for our patients.

Citation: Velayos M, Estefanía K, Álvarez M, Sarmiento MC, Moratilla L, Sanabria P, Hernández F, López Santamaría MV. Healthcare staff as promoters of parental presence at anesthetic induction: Net Promoter Score survey. *World J Clin Pediatr* 2021; 10(6): 159-167
URL: https://www.wjgnet.com/2219-2808/full/v10/i6/159.htm
DOI: https://dx.doi.org/10.5409/wjcp.v10.i6.159

INTRODUCTION

Surgical interventions are traumatic events that causes stress and anxiety in the pediatric patient and the family environment. Several studies have shown that this type of anxiety is related to undesirable events such as negative results of anesthetic induction, increased pain in the postoperative period, increased postsurgical delirium, decreased adherence to subsequent medical treatment, and behavioral changes including sleep disorders, nutritional problems, enuresis, fear of separation, and aggression[1-4]. Various strategies have been developed to mitigate presurgical anxiety in both children and their family environment, with variable results that are controversial and difficult to evaluate. The use of pharmacological interventions remains one of the most widely used tools. However, in recent years, the use of nonpharmacological measures has gained great relevance in this field, with parental presence during induction of anesthesia (PPIA) being one of the most discussed[5].

It has been reported that families prefer to participate and be present during high-stress procedures such as surgery, and those who are present generally report favorable experiences and even consider it a right[6,7]. This trend, along with the increasing development of patient- and family-centered care (PFCC), the basic concepts of which include participation and collaboration, is often objectionable to those who do not favor active participation of the patient and family in the surgical experience. Critics usually argue that a PPIA program requires additional staff and new infrastructure, increased surgical time and therefore decreased operating room efficiency, increased costs, and possible medical-legal issues[9,10]. However, there are no validated data to support those arguments, and an increasing number of hospitals are implementing this measure, with good acceptance by health staff. The objective of

P-Reviewer: Ghannam WM, Kvolik S, Mondardini MC
S-Editor: Liu M
L-Editor: Filipodia
P-Editor: Yuan YY

this study was to evaluate the perceptions of health care personnel regarding the implementation of the PPIA program in our center.

MATERIALS AND METHODS

PPIA implementation program

Implementation of the PPIA program was motivated by the pediatric surgery and child anesthesia and resuscitation services at our center to achieve more patient- and family-centered medicine and after having positive experience with the same program in other centers at our medical center.

The program was implemented in June 2019 after approval by the ethics committee. The necessary space for the different phases of the program were set up, all the necessary material for the entrance to the operating room was obtained, and all the personnel involved were properly instructed in every step of the process. A pilot phase was initiated with 57 patients undergoing major outpatient surgery without the need for hospitalization (*e.g.*, epigastric herniorrhaphy, umbilical herniorrhaphy, inguinal herniorrhaphy, circumcision, hydrocelectomy, orchidopexy, and other minor surgical procedures). A future objective of this measure is potentially extending it to children undergoing conventional inpatient surgery and invasive diagnostic-therapeutic tests such as magnetic resonance imaging, computed tomography, and interventional radiology. The participating patients were between 2 and 12 years of age, were classified as American Society of Anesthesiologists status I, and 48% were premedicated with oral midazolam depending of the criteria used by the responsible anesthesiologist.

Process

The possibility of PPIA was offered to all parents or legal guardians of children cited for major outpatient surgery. The decision to be present or absent was made voluntarily by the parents or legal guardians, as was the choice of the person who would accompany the patient if there were several companions. Those who agreed to be present during anesthetic induction were given a set of rules and instructions to follow. (1) The dress code required a surgical suit, surgical cap, shoe covers, and face mask; (2) Do not touch anything, only the child, the bed, or the anesthetic mask in case of receiving the order from the anesthesiologist. (3) The phases of the process included preparation in the day hospital; moving to the presurgery room and the operating room, anesthetic induction, which includes an excitation phase with possible involuntary patient movement and hypotonia; and finally leaving the operating room. (4) The immediate postoperative phase included giving advice and instructions to understand and assist in patient recovery. The benefits and positive points of the process, such as the importance of focusing all attention on the child and the help and cooperation received from the family member at a critical time such as anesthetic induction, were reinforced at all times.

Survey

An internal survey was sent by email to all healthcare personnel involved in the process (*i.e.* pediatric surgeons, pediatric anesthesiologists, nursing and other medical staff) during the month of November 2019. The survey was composed of 14 items that were subdivided into positive aspects for PPIA and negative aspects for PPIA. The responses were graded on a Likert scale that ranged from totally disagree (1) to totally agree (5). The same questionnaire collected the demographic data of the respondents including age, gender, and the health group to which they belonged. The survey results were interpreted by the Net Promoter Score (NPS), which is a quality indicator that measures customer loyalty to companies based on recommendations. In the original version, each item has a score of from 0 to 10 where 0 is very unlikely to be recommended and 10 is strongly recommended. Scores between 9 and 10 are classified as promoters, those between 7 and 8 are passive, and those ≤ 6 are detractors. The final score is obtained by subtracting the detractors from the promoters and obtaining a percentage ranging from −100 to 100 that measures the quality of service, where an score > 0 is good, a score > 50 is excellent and a negative NPS is not a recommendation [11].

After obtaining the Likert scale scores for each item, these were transformed into values used by the NPS. Thus, scores of 4 or 5 on the Likert scale were considered as 9 or 10 in the NPS and were therefore promoters. Scores of 1 or 2, were considered as ≤ 6 and were therefore detractors. Finally, scores of 3 on the Likert scale were considered

as 7 or 8 on the NPS, were passive, and were not taken into account in the study. After the total numbers and percentages of promoters and retractors in percentage for each item of the questionnaire were obtained, the percentage of promoters was subtracted from the percentage of retractors of each item of the survey. An NPS > 0% indicated good quality, an NPS > 50% indicated excellent quality, and an NPS < 0% indicated poor quality. Finally, a statistical analysis was comparing the demographic characteristics and survey responses of each group was performed. Responses of < 75% were excluded.

Statistical analysis

The data were collected using Microsoft Excel version 16.35. Statistical analysis was performed with the IBM SPSS 25.0 statistical package. Quantitative variables were reported as means and standard deviation and qualitative variables as absolute frequencies and percentages. After checking the normality of distributions of the variables with the Kolmogorov-Smirnoff test (corrected by the Lilliefors test), quantitative variables were compared with the *t*-test and categorical variables with the chi-square test or the *F*-test. A P value of < 0.05 was considered significant; all intervals were calculated with 95% confidence.

RESULTS

The survey was sent to 141 people; the response rate was 69%. The group with the highest participation was nursing, with 30% of the total respondents, followed by pediatric surgeons (27%), and other medical staff (27%), and pediatric anesthesiologists (16%, Figure 1). Of the total number of responses, 68% were women and 32% were men. The average age was 42.3 ± 10.6 years. The demographic data for each group are shown in Table 1.

Answers to the survey sent to the healthcare staff

Table 2 shows the percentages of promoters, retractors and passive respondents as well as the NPS results. Table 3 shows the percentage of promoters in each group for each question and the comparative analysis of group responses. Questions rated positive for PPIA had NPS values > 50 (excellent service quality), except for the question "PPIA decreases use of presurgical medication" which had an NPS of between 0 and 50 (good service quality), meaning that 100% of respondents agreed fully and agreed with the positive aspects of PPIA. On the other hand, all questions considered negative for PPIA had a negative NPS (poor quality of service), meaning that the respondents all disagreed that PPIA has negative aspects for the patients, their families, and for the development of surgical care activities. Comparing the results by group, statistically significant differences were found only for the question "PPIA increases patient safety," with a lower percentage of pediatric surgeons who think that PPIA increases patient safety, compared with anesthetists (69.6% *vs* 90%), nurses (69.6% *vs* 92%), and other medical staff (69.6% *vs* 90% *vs* 96%, $P = 0.037$).

DISCUSSION

The results of our survey showed full approval of the implementation of the PPIA program at our center. The intervention was considered by pediatric surgeons, anesthesiologists, nurses, and other medical staff as an excellent quality service by more than 80% of the respondents. This conclusion is in line with other recent studies that showed that pediatric surgery departments and other healthcare providers approved of PPIA and consider it beneficial for the patient[7,12]. To our best knowledge, this is the first study to investigate whether sex and age were possible conditioning factors in answering this type of survey. According to our results, women were more prone to respond than men, but we did not find any differences regarding the age of the respondents. That finding might be explained by the higher percentage of women in the group with more survey participants (93% women *vs* 7% men), and not as a factor involved in support or resistance to PPIA.

We launched the project because we consider the presence of parents during anesthetic induction as part of a comprehensive, family-centered approach that respects their requirements and decisions. That was not always the case in pediatric healthcare. In 1895 D'Arcy Power wrote: "When an operation has been decided upon,

Table 1 Demographic data of each group

	Pediatric surgeons	Pediatric anesthesiologists	Nursing	Other medical staff	*P* value
Age, yr	40.8 ± 11.5	43 ± 8.5	41.7 ± 9.8	44.2 ± 11.7	0.56
Age subgroups, yr					
< 50	70	83	79	73	0.77
> 50	30	17	21	27	
Gender					
Male	46	44	7	38	0.006
Female	54	56	93	62	

Data are means ± SD or percentages.

Table 2 Percentages of promoters, retractors, and passive responses in each group for each question and the Net Promoter Score (promoters − retractors) for each question

Survey question	Promotors	Retractors	Passive	NPS (promotors − retractors)
Positive for PPIA				
PPIA improves the child's surgical experience	83.5	13.4	3.1	70.1
PPIA improves the parent's surgical experience	81.4	6.2	12.4	75.2
PPIA improves the relationship of the patient and his/her environment with health professionals at all levels	81.4	4.2	14.4	77.2
PPIA increases parental satisfaction	82.5	3	14.4	79.5
PPIA increases patient safety	71.1	11.3	17.5	59.8
PPIA decreases the use of presurgical medication	47.4	19.6	33	27.8
Negative for PPIA				
PPIA decreases surgical efficiency	5.1	71.1	23.7	-66
PPIA should be exclusive por patients in ambulatory surgery	12.4	71.1	6.2	-58.7
PPIA increases parental anxiety	23.7	54.6	21.6	-30.9
PPIA increases child's anxiety	3.1	86.6	10.3	-83.5
PPIA increases the duration of anesthetic induction	16.5	54.6	28.8	-38.1
PPIA increases the number of infections	4.1	63.9	32	-59.8
PPIA increases the cost of health care	20.6	59.8	19.6	-39.2
PPIA increases fear of legal problems	24.7	52.6	23.7	-27.9

NPS: Net Promoter Score; PPIA: Parental presence at anesthetic induction.

it will generally be seen that better results are obtained if the child is removed from his usual environment and placed in the care of those who have special experience in the care of sick children"[13]. The idea of separating the pediatric surgical patient from the family environment was maintained during the first half of the 20th century. Later, Gross[14] and Caniano *et al*[15] emphasized and assumed the role of the family in the child's surgical experience. It has been in recent decades that PFCC has grown and evolved to become a goal to be achieved in all medical areas including pediatric surgery[8]. Participation and collaboration are the basic concepts of PFCC, and numerous studies have tested strategies such as preoperative family preparation or the impact of the PPIA. The data on family preparation for the reduction of preoperative anxiety are positive[16,17]; in contrast, the results obtained regarding the impact of PPIA are controversial and not clear, as the latest Cochrane review showed[5]. However, even though Sadeghi *et al*[18] and Hussain and Khan[19] found no benefit of

Table 3 Percentage of promoters in each group for each question and comparative analysis by group

Survey question	Pediatric surgeons	Pediatric anesthesiologist	Nursing	Other medical staff	*P* value
Positive for PPIA					
PPIA improves the child's surgical experience	95	100	92	100	0.36
PPIA improves the parent's surgical experience	83	100	92	100	0.07
PPIA improves the relationship of the patient and his/her environment with health professionals at all levels	86	100	96	100	0.11
PPIA increases parental satisfaction	85	100	100	96	0.07
PPIA increases patient safety	70	90	92	96	$P < 0.05$
PPIA decreases the use of presurgical medication	62	80	55	88	0.11
Negative for PPIA					
PPIA decreases surgical efficiency	12	8	0	12	0.45
PPIA should be exclusive por patients in ambulatory surgery	13	23	8.3	22	0.52
PPIA increases parental anxiety	38	31	36	14	0.27
PPIA increases child's anxiety	0	0	7	3	0.45
PPIA increases the duration of anesthetic induction	29	21	23	22	0.94
PPIA increases the number of infections	5	10	11	11	0.91
PPIA increases the cost of health care	19	25	36	19	0.50
PPIA increases fear of legal problems	37	21.4	37	32	0.77

PPIA: Parental presence at anesthetic induction.

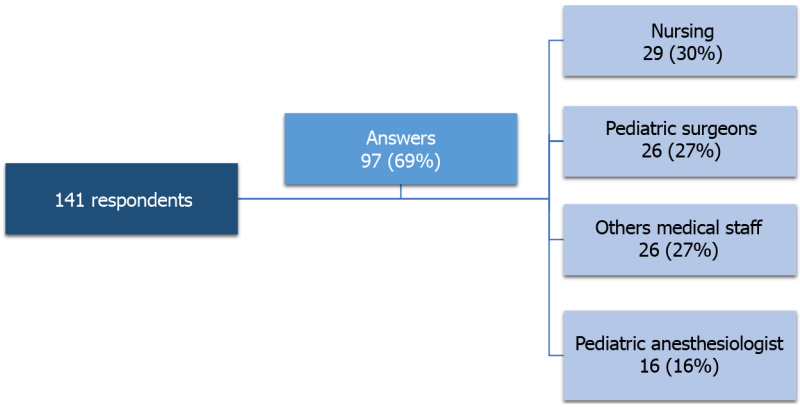

Figure 1 Survey participants. Ninety-seven of 141 healthcare workers who were sent the survey (69%) returned it with answers. The total number of participants and total number of participants in each group are shown.

PPIA with respect to preoperative anxiety, they did find other positive aspects, such as improved patient cooperation at the time of anesthetic induction, better acceptance of the face mask, or increased parental satisfaction, suggesting that PPIA may improve those aspects. In line with those findings, we found that the group with the highest percentage of promoters in most of the positive questions for PPIA was pediatric anesthesiologists, probably because behavior of children during anesthetic induction was better when a parent was present. However, Luehmann *et al*[7], showed that the median response to PPIA was most favorable for perioperative nurses, who are involved in all aspects of patient care and can give a more comprehensive opinion. The findings reinforce the support to the program from different points of view of the same process.

Many prejudices had to be overcome before the project could be launched. There are still common points of contention against this measure on the part of the medical staff, who believe that the presence of the parents could be disturbing, the induction of anesthesia and surgical intervention delayed, and the possibility of generating medical-legal problems. For example, Paice *et al*[6] reported significantly less support from medical staff for the presence of parents during invasive procedures compared with parents. In our results, pediatric surgeons were less positive than other groups when asked whether PPIA increased patient safety, which could be explained by fear of unwanted events. However, no related adverse effects were found in other studies, and there are no valid arguments to justify medical staff resistance to the implementation of this measure.

Unfortunately, despite the rationale and supporting evidence, PPIA is far from being a widespread and applicable procedure for all surgical procedures and invasive testing. Pediatric surgery has changed enormously over the last century, and we believe that family involvement in day-to-day clinical practice will eventually become a well-established part of pediatric surgical patient care. Finally, the acceptance and commitment of the healthcare personnel in the application of the PPIA at our center is highlighted. We suggest that all surgical centers should have programs that include family involvement, such as parental presence at anesthetic induction.

Limitations

Our study has the typical limitations of a qualitative survey. We cannot draw objective conclusions that can be tested if we do not offer an in-depth understanding of the acceptance of PPIA at our center with the belief in its expansion to other centers. Although we included the sex and age of respondents, other influential factors such as years of experience or previous experience with PPIA programs were not included in the analysis. We also did not take passive responses into account, assuming that they would not be relevant to the results. Finally, we are aware of the difficulty of applying a quality score from the business world to a measure of preoperative anxiety, but we believe in it here.

CONCLUSION

The results highlight the acceptance and commitment of healthcare personnel in the application of the PPIA in our center. We suggest that all surgical centers should have programs that include family involvement, such as parental presence at anesthesia induction.

ARTICLE HIGHLIGHTS

Research background

Medicine is getting closer and closer to the human side of the patient and family. Family knowledge, understanding, and accompanying their children, offers them an opportunity to contribute in the surgical process, and helps to reduce the stress caused by those situations.

Research motivation

We were motivated by the importance of avoiding the anxiety and stress that a surgical intervention causes in pediatric patients and their family environment, improving our relationship with them, and promoting their welfare.

Research objectives

The objective was to analyze the responses of healthcare workers to the implementation of a program in which parents accompany their children to the operating room to mitigate and reduce the anxiety and stress produced in the patient and their family environment by surgical interventions.

Research methods

A survey was designed and sent to the personnel involved in the process. It was analyzed and reinterpreted by applying a novel "Net Promoter Score".

Research results

The personnel involved in the process support the implementation of the program

Research conclusions

Based on the good acceptance of the program in our center, we suggest the development and implementation of the program by other centers.

Research perspectives

More studies are needed to demonstrate the effectiveness of parental presence during the induction of anesthesia (PPIA) and the support of healthcare workers for measures such as PPIA or similar programs. We must demonstrate the importance and involvement in achieving patient and patient- and family-centered care as one of the goals of present and future medicine.

ACKNOWLEDGEMENTS

The authors would like to thank all the health personnel who have supported and made possible the development and implementation of this program.

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2021 November 9; 10(6): 168-176

DOI: 10.5409/wjcp.v10.i6.168

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Observational Study

Association of breastfeeding with tidal breathing analysis in infants with bronchiolitis

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Institutional review board statement: The Institutional Review Board of University

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Abstract

BACKGROUND

Tidal breathing flow-volume (TBFV) analysis provides important information about lung mechanics in infants.

AIM

To assess the effects of breastfeeding on the TBFV measurements of infants who recover from acute bronchiolitis.

METHODS

In this cross-sectional study, TBFV analysis was performed in infants with bronchiolitis prior to hospital discharge. The ratio of time to peak expiratory flow to total expiratory time (tPEF/tE) at baseline and after the administration of 400 mcg salbutamol was evaluated.

RESULTS

General Hospital of Alexandroupolis provided approval for this study (IRB No. 23927/2382/02.01.2017).

Informed consent statement: Parental approval was obtained prior to inclusion for all involved infants.

Conflict-of-interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data sharing statement: The authors confirm that the data supporting the findings of this study are available within the article and its tables/figures. Raw data, without patient's personal information, are available upon reasonable request from the corresponding author.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Specialty type: Pediatrics

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0

A total of 56 infants (35 boys), aged 7.4 ± 2.8 mo, were included. Of them, 12.5% were exposed to tobacco smoke and 41.1% were breastfed less than 2 mo. There were no differences in baseline TBFV measurements between the breastfeeding groups; however, those who breastfed longer than 2 mo had a greater change in tPEF/tE after bronchodilation (12% ± 10.4% *vs* 0.9% ± 7.1%; $P < 0.001$). Moreover, there was a clear dose-response relationship between tPEF/tE reversibility and duration of breastfeeding ($P < 0.001$). In multivariate regression analysis, infants who breastfed less (regression coefficient -0.335, $P = 0.010$) or were exposed to cigarette smoke (regression coefficient 0.353, $P = 0.007$) showed a greater change in tPEF/tE after bronchodilation, independent of sex, prematurity, and family history of asthma or atopy.

CONCLUSION

Infants who recover from bronchiolitis and have a shorter duration of breastfeeding or are exposed to cigarette smoke, have TBFV measurements indicative of obstructive lung disease.

Key Words: Tidal breathing analysis; Lung function; Bronchiolitis; Breastfeeding; Cigarette smoke; Infants

Core Tip: Assessment of lung function using tidal breathing could be beneficial for infants and preschoolers in whom forced respiratory maneuvers cannot be performed. We examined the correlation between breastfeeding and tidal breathing analysis in infants with bronchiolitis, and demonstrated that those who were exposed to cigarette smoke and/or had a shorter duration of breastfeeding showed tidal breathing alterations indicative of obstructive pulmonary disease.

Citation: Perikleous E, Fouzas S, Karageorgiou A, Steiropoulos P, Nena E, Chatzimichael A, Tsalkidis A, Paraskakis E. Association of breastfeeding with tidal breathing analysis in infants with bronchiolitis. *World J Clin Pediatr* 2021; 10(6): 168-176
URL: https://www.wjgnet.com/2219-2808/full/v10/i6/168.htm
DOI: https://dx.doi.org/10.5409/wjcp.v10.i6.168

INTRODUCTION

Bronchiolitis is a viral infection of lower airways that is characterized by substantial inflammation, increased mucus production, and necrosis of small airway epithelial cells[1]. It is the leading cause of infant morbidity and mortality worldwide[2], and represents a significant burden for the healthcare system, the family, and society[3]. Infants with co-existing conditions, such as prematurity and cardiopulmonary disorders, are at higher risk of developing more severe bronchiolitis[3]. Moreover, environmental factors such as smoking exposure, indoor and outdoor pollution[4], and lack of breastfeeding[5] may significantly increase susceptibility to the disease.

The favorable effects of breastfeeding are indisputable, and no other practice can drastically promote infant's health in the short- and long-term[6]. Comprehensively, there is some evidence of the consistent advantageous impact of breastfeeding on increasing forced vital capacity (FVC)[7]. Early life nutrition with breast milk as the initial food for newborns is considered 'the best' due to its beneficial effects on overall health, along with improved lung function. A previous study showed a link between breastfeeding and lung function in school-age children, namely, greater forced expiratory flow at 50% (FEF50), particularly in those who breastfed longer than 3 mo including children of mothers with asthma[8]. Regarding bronchiolitis, current evidence suggests that breastfed infants have a clear immunological advantage compared with their formula-fed peers[9]; exclusive breastfeeding has been shown to decrease the requirement for oxygen supplementation, the length of hospital stay, and the risk of respiratory failure in infants with more severe forms of the disease[9]. However, despite the clear clinical advantages, less is known about the effects of

Grade E (Poor): 0

Received: May 9, 2021
Peer-review started: May 9, 2021
First decision: June 17, 2021
Revised: June 30, 2021
Accepted: October 25, 2021
Article in press: October 25, 2021
Published online: November 9, 2021

P-Reviewer: Rodrigues AT
S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC

breastfeeding on the pulmonary function of infants with acute bronchiolitis.

There is some evidence indicating that tobacco smoke exposure in children decreases lung function and augments airway hyperresponsiveness, predisposing infants to a more severe clinical course of infection compared to unexposed peers[4]. Similarly, studies have shown that maternal smoking during pregnancy is related to bronchiolitis[4,10]. Overall, pregnancy and subsequent parenthood can become major motivators for mothers and caregivers to permanently quit this detrimental practice.

Although lung function testing at bedside is notoriously difficult in infancy[11], recent evidence suggests that tidal breathing flow-volume (TBFV) measurement and analysis are feasible[11,12]. In particular, the ratio of time to peak expiratory flow to total expiratory time (tPEF/tE) decreases in obstructive lung disorders[10], providing important information on the underlying pathophysiological mechanisms and extent of lung injury[11,12].

The aim of this study was to assess the effects of breastfeeding on the lung function of infants who recovered from acute bronchiolitis. We hypothesized that breastfeeding may have favorable effects on baseline tPEF/tE values and/or tPEF/tE reversibility after bronchodilation, independent of other confounding factors.

MATERIALS AND METHODS

Patients

This observational, cross-sectional study was performed between September 2016 and April 2018 in the Pediatric Department of the University General Hospital of Alexandroupolis (Alexandroupolis, Greece). All infants aged 2-12 mo and hospitalized with bronchiolitis were eligible to participate. Bronchiolitis was defined according to the relevant history and physical examination (fever, cough, tachypnoea, chest recession, wheeze or crackles during auscultation)[3]. Infants with genetic disorders, neuromuscular disorders, craniofacial abnormalities, congenital heart disease, a history of significant prematurity (born at < 32 wk gestational age), or requiring intubation and mechanical ventilation after birth were excluded. The study was approved by the local ethics committee, and parental informed consent was obtained prior to enrollment.

Procedures

On the day of hospital discharge, eligible infants underwent TBFV measurements in the pediatric lung function laboratory using the MasterScreen pediatric respiratory system (Jaeger/CareFusion, Hoechberg, Germany). All infants were tested according to relevant European Respiratory Society/American Thoracic Society guidelines[13-15] during natural sleep after feeding. A minimum of 30 s of natural breathing was recorded to acquire a set of at least 10 regular breaths. The ratio of tPEF/tE was automatically calculated by the system at baseline and 10 min after the administration of 300 mcg salbutamol inhaler *via* an appropriate holding chamber. The metadata of the study population were obtained from the medical records. The weight-for-length *z*-scores were estimated using Centers for Disease Control and Prevention/National Center for Health Statistics norms[16].

Statistical analyses

Continuous variables are expressed as the mean ± SD standard deviation and compared with the Student's *t*-test or one-way analysis of variance (multiple comparisons). Multivariate regression analysis was used to determine the outcome of breastfeeding in terms of gender, history of prematurity, and family history of atopy. All analyses were performed using IBM SPSS version 25 (IBM Corp., Armonk, NY, United States).

RESULTS

A total of 56 infants (35 boys), aged 7.4 ± 2.8 mo, were included in this study. Their characteristics are presented in Table 1. Of them, 21.4% were born prematurely, 12.5% were exposed to tobacco smoke (during pregnancy and/or after birth), and 16.1% had a family history of asthma or atopy. No breastfeeding was reported in 7 infants (12.5%), whereas 23 infants (41.1%) were breastfed less than 2 mo (Table 1).

There were no differences in baseline TBFV measurements between infants who did not breastfeed or breastfed less than 2 mo (Group 1) and those who breastfed longer

Table 1 Characteristics of the study population

Characteristics	
n	56
Age (mo)	7.4 ± 2.8
Male sex, *n* (%)	35 (62.5)
Body weight, kg	7.3 ± 1.6
Body length, cm	65 ± 8.1
Weight-for-length *z*-score	-0.2 ± 2.0
Gestational age, wk	37.9 ± 1.5 (range 35-41)
Prematurity (< 37 wk)	12 (21.4)
Breastfeeding	
No	7 (12.5)
< 2 mo	16 (28.6)
2-6 mo	12 (21.4)
> 6 mo	21 (37.5)
Smoking exposure	
In pregnancy	5 (8.9)
After birth	7 (12.5)
In pregnancy and/or after birth	7 (12.5)
Family history of asthma/atopy	9 (16.1)

Values are mean ± SD or number of cases (%).

than 2 mo (Group 2) (Table 2). Conversely, infants in Group 1 had a significantly higher change in tPEF/tE after bronchodilation compared with those in Group 2 (12% ± 10.4% *vs* 0.9% ± 7.1%; $P < 0.001$) (Figure 1A). The tPEF/tE reversibility was also higher in infants exposed to tobacco smoke during pregnancy and/or after birth (Figure 1B). There was a clear dose-response relationship between the reversibility of tPEF/tE and the duration of breastfeeding ($P < 0.001$) (Figure 2).

Multivariate regression analysis showed that infants who breastfed less (beta -0.335, $P = 0.010$) or were exposed to cigarette smoke (beta 0.353, $P = 0.007$) had a greater change in tPEF/tE after bronchodilation, independent of sex, prematurity, and family history of asthma or atopy (Table 3).

DISCUSSION

In this study, we demonstrated that infants who recovered from acute bronchiolitis and had a shorter duration of breastfeeding or were exposed to cigarette smoke, had TBFV measurements indicative of obstructive lung disease. Specifically, these infants had a greater percent change in tPEF/TE after bronchodilation, and this effect was independent of other confounding factors such as premature birth and family history of asthma or atopy. Interestingly, there was a clear dose-response relationship between tPEF/tE reversibility and the duration of breastfeeding. Moreover, infants who were exposed to cigarette smoke showed a greater change in tPEF/tE after bronchodilation, independent of sex, prematurity, and family history of asthma or atopy.

Early life exposures may affect the outgrowth of pulmonary system, resulting in an immediate impact on later lung function. Previous studies have highlighted the key role of breastfeeding in terms of larger lung volumes at school age[8,17], suggesting the influence of breastfeeding on respiratory health. In addition, studies have shown that extended and exclusive breastfeeding reduces the risk of wheezing and asthma during infancy, early childhood[17-20], and even in youth[21], functioning as a shield against allergic predisposition. In a recent study of 555 children, forced expiratory volume in 1 s and FVC markedly increased in accordance with breastfeeding duration

Table 2 Baseline tidal breathing flow-volume values according to breastfeeding duration

	BF < 2 mo (*n* = 23)	BF ≥ 2 mo (*n* = 33)	*P* value
Tidal volume, mL/kg	8.6 ± 1.8	8.3 ± 2.1	0.580
Respiratory rate, bpm	46.8 ± 20	44.7 ± 18.4	0.687
Expiratory time, s	0.57 ± 0.21	0.55 ± 0.22	0.735
tPEF/tE, %	35.4 ± 15.5	41.3 ± 13.7	0.139

Values are mean ± SD. BF: Breastfeeding; TBFV: Tidal breathing flow-volume; tPEF/tE: Time to peak expiratory flow to total expiratory time.

Table 3 Factors affecting the % time to peak expiratory flow to total expiratory time change after bronchodilation

	Regression coefficient β	*P* value
Breastfeeding duration	-0.335	0.010
Cigarette smoke exposure	0.353	0.007
Male sex	0.005	0.974
Prematurity	0.031	0.833
Family History of asthma/atopy	0.121	0.379

Multivariable linear regression analysis; the effects of the independent variables were adjusted for each other. tPEF/tE: Time to peak expiratory flow to total expiratory time.

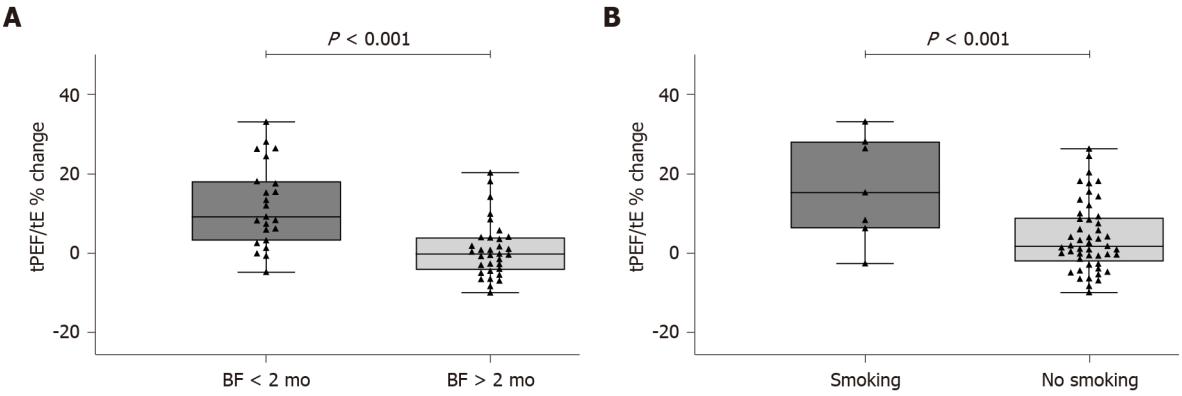

Figure 1 Percent change in time to peak expiratory flow to total expiratory time after bronchodilation in relation to breastfeeding and smoking exposure. A: Breastfeeding; B: Smoking exposure. BF: Breastfeeding; tPEF/tE: Time to peak expiratory flow to total expiratory time.

in those with asthma group[20]. However, in a novel birth cohort of 377 healthy term infants, a link between breastfeeding duration and obstructive or restrictive lung function was not shown[22]. Similarly, in a birth cohort of 620 infants, lung function was assessed at 12 and 18 years of age; duration of breastfeeding did not greatly influence lung function in children with a positive family history for allergic diseases [23]. Thus, whether breastfeeding protects against allergic disease in childhood remains a subject of debate, although exclusive breastfeeding for a duration of 6 mo is the keystone for the promotion of allergy health.

The evaluation of pulmonary function by TBFV analysis has certain benefits in infants in whom forced respiratory flows cannot be performed. Several studies have examined the application of TBFV measurements in a variety of lung disorders and have shown that a reduction in tPEF/tE ratio is suggestive of airway obstruction[11,12,15,24-26]. Zedan *et al*[25] reported that wheezing infants with a positive family history of asthma or who had never been breastfed, displayed significantly lower tPEF/tE compared with healthy controls. Similarly, children and infants with wheezing disorders have a reduced tPEF/tE ratio compared with control subgroups[27,28]. Moreover, studies of infants with chronic lung disease showed impaired lung

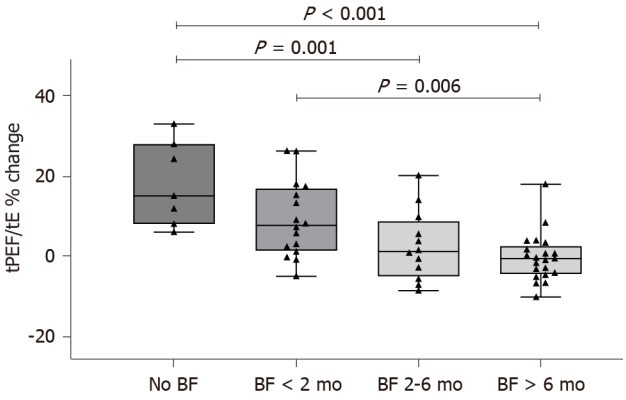

Figure 2 Percent change in time to peak expiratory flow to total expiratory time after bronchodilation in relation to the duration of breastfeeding. BF: Breastfeeding; tPEF/tE: Time to peak expiratory flow to total expiratory time.

compliance and reduced resistance during the first 12 mo of life[29].

Qi *et al*[30] found that wheezing infants had reduced lung function compared with those who were not wheezing, and that tPEF/tE was negatively associated with later poor respiratory outcomes; the deficit in tPEF/tE ratio remained after clinical improvement. However, a study in school-age children with asthma[24] showed no difference in tidal breathing parameters compared with control groups.

In accordance with our main findings, in a preliminary Norwegian study of infants with acute bronchiolitis, the tPEF/tE was reduced but improved after the administration of inhaled adrenaline[31]. By contrast, in another study in infants with bronchiolitis, the researchers did not find any significant differences in tPEF/tE after the administration of nebulized albuterol[32]. In a recent cross-sectional study, tPEF/tE was inversely related to the length of hospital stay and disease severity in infants with bronchiolitis[33], and was also significantly reduced in children exposed to parental smoking[33]. In another study of preschool wheezers, family history of asthma, breastfeeding duration less than 3 mo, and passive smoking, were all significant risk factors for bronchial hyperresponsiveness, defined as tPEF/tE increase > 20% following salbutamol administration[34].

Our study had a number of limitations. First, it was a single-center study with a small sample size; thus the findings cannot be generalized to all populations. Second, a control group was not included in the study design; consequently we could not compare our results with a subgroup of healthy peers. Third, the study design did not include some relevant confounding factors that could affect lung function, such as air pollution.

CONCLUSION

Infants who recovered from acute bronchiolitis and had a shorter duration of breastfeeding or were exposed to cigarette smoke, had TBFV measurements indicative of obstructive lung disease. Tidal breathing is undeniably a complex process, but its measurement during infancy appears promising. To understand the mechanisms by which acute bronchiolitis may affect lung function in infancy and beyond, additional large-scale research is required.

ARTICLE HIGHLIGHTS

Research background

Bronchiolitis is a common viral infection of lower airways and a major cause of morbidity and mortality globally, especially among infants with concomitant medical conditions. The positive effects of breastfeeding are uncontested in infant's health in the short- and long-term.

Research motivation

There are sufficient data suggesting the advantageous effects of breastfeeding on pulmonary function, but less information regarding the influence of breastfeeding on lung function in infants with acute bronchiolitis.

Research objectives

To assess the effects of breastfeeding on tidal breathing flow-volume (TBFV) measurements of infants who recovered from acute bronchiolitis.

Research methods

TBFV analysis was conducted in 56 infants with bronchiolitis prior to hospital discharge. The ratio of time to peak expiratory flow to total expiratory time (tPEF/tE) at baseline and after the administration of 400 mcg salbutamol was assessed using a MasterScreen pediatric respiratory system (Jaeger/CareFusion, Hoechberg, Germany). All infants were tested according to European Respiratory Society/American Thoracic Society guidelines in the middle of natural sleep following feeding. Multivariate regression analysis was used to investigate the outcome of breastfeeding in terms of gender, history of prematurity, and family history of atopy. All analyses were conducted in IBM SPSS version 25.

Research results

There were no differences in baseline TBFV measurements between breastfeeding groups; however, children who breastfed less than 2 mo had a greater tPEF/tE change after bronchodilation (12% ± 10.4% *vs* 0.9% ± 7.1%; $P < 0.001$). Additionally, a distinct dose-response relationship between tPEF/tE reversibility and duration of breastfeeding was shown ($P < 0.001$). In multivariable regression analysis, infants who breastfed less (beta -0.335, $P = 0.010$) or were exposed to cigarette smoke (beta 0.353, $P = 0.007$) exhibited a higher tPEF/tE change after bronchodilation, irrelevant of sex, prematurity, and family history of asthma or atopy.

Research conclusions

Infants who recovered from acute bronchiolitis and had a shorter duration of breastfeeding or were exposed to cigarette smoke, had TBFV analyses indicative of obstructive lung disease, independently of other confounding factors. Tidal breathing is undoubtedly a complicated procedure, but its measurement during infancy is promising.

Research perspectives

Additional large-scale studies are required to determine the mechanisms by which acute bronchiolitis may affect lung function in early infancy as well as later in life.

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World J Clin Pediatr 2021 November 9; 10(6): 177-191

DOI: 10.5409/wjcp.v10.i6.177

ISSN 2219-2808 (online)

META-ANALYSIS

Prevalence of pulmonary hypertension among children with Down syndrome: A systematic review and meta-analysis

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Conflict-of-interest statement: All the authors declare that they have no competing interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Abstract

BACKGROUND

Pulmonary hypertension (PH) has serious short- and long-term consequences. PH is gaining increasing importance in high risk groups such as Down syndrome (DS) as it influences their overall survival and prognosis. Hence, there is a dire need to collate the prevalence rates of PH in order to undertake definitive measures for early diagnosis and management.

AIM

To determine the prevalence of PH in children with DS.

METHODS

The authors individually conducted a search of electronic databases manually (Cochrane library, PubMed, EMBASE, Scopus, Web of Science). Data extraction and quality control were independently performed by two reviewers and a third reviewer resolved any conflicts of opinion. The words used in the literature search were "pulmonary hypertension" and "pulmonary arterial hypertension"; "Down syndrome" and "trisomy 21" and "prevalence". The data were analyzed by Comprehensive Meta-Analysis Software Version 2. Risk of bias assessment and STROBE checklist were used for quality assessment.

RESULTS

Of 1578 articles identified, 17 were selected for final analysis. The pooled prevalence of PH in these studies was 25.5%. Subgroup analysis was carried out for age, gender, region, year of publication, risk of bias and etiology of PH.

CONCLUSION

This review highlights the increasing prevalence of PH in children with DS. It is crucial for pediatricians to be aware of this morbid disease and channel their

Specialty type: Pediatrics

Country/Territory of origin: India

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 19, 2021
Peer-review started: January 19, 2021
First decision: May 6, 2021
Revised: May 13, 2021
Accepted: August 17, 2021
Article in press: August 17, 2021
Published online: November 9, 2021

P-Reviewer: Tommasini A
S-Editor: Ma YJ
L-Editor: Webster JR
P-Editor: Yuan YY

efforts towards earlier diagnosis and successful management. Community-based studies with a larger sample size of children with DS should be carried out to better characterize the epidemiology and underlying etiology of PH in DS.

Key Words: Down syndrome; Pulmonary hypertension; Prevalence; Trisomy 21; Persistent pulmonary hypertension; Congenital heart disease

Core Tip: The objective of this review is to provide quantitative data on the prevalence of pulmonary hypertension (PH) in pediatric patients with Down syndrome (DS). In addition, we also wish to address the lack of consensus on screening guidelines for PH in DS, as it is frequently missed unless associated with an underlying congenital heart disease. We conclude that children with DS require early echocardiography irrespective of an underlying congenital heart disease. We, therefore, by means of this systematic review would like to increase the vigilance for PH in DS, with the ultimate goal of reducing the morbidity due to PH in these children.

Citation: Taksande A, Pujari D, Jameel PZ, Taksande B, Meshram R. Prevalence of pulmonary hypertension among children with Down syndrome: A systematic review and meta-analysis. *World J Clin Pediatr* 2021; 10(6): 177-191
URL: https://www.wjgnet.com/2219-2808/full/v10/i6/177.htm
DOI: https://dx.doi.org/10.5409/wjcp.v10.i6.177

INTRODUCTION

Down syndrome (DS) was first clinically observed and described by Dr. Down[1] in his report on the "Observations on an ethnic classification of idiots" in 1866. The incidence of DS is approximately 1 in every 733 live births, which makes it the most common human malformation[2,3]. Children with DS are at an increased risk of developing pulmonary hypertension (PH). DS is the most common genetic syndrome associated with PH (with or without congenital heart disease), the others being DiGeorge syndrome, Scimitar syndrome, Noonan syndrome, Dursun syndrome and Cantu syndrome[4]. Regardless of the underlying etiology, PH has debilitating consequences on the health of the child and also reduces life expectancy. Approximately 75% of all deaths in DS may be attributed to pneumonia and infectious lung disease, congenital heart disease (CHD) and circulatory disease (vascular diseases such PH)[5]. There have been no studies estimating the precise disease burden of PH in children with DS even though PH is independently associated with death among children with DS[6]. This reflects the need to provide a multidisciplinary approach for children with DS and PH for better management. Recent recommendations from the pediatric task force of the 6th World Symposium on Pulmonary Hypertension (WSPH) have defined PH in the pediatric age group as a resting mean pulmonary artery pressure (mPAP) > 20 mmHg (decreased from 25 mmHg) in children greater than 3 months of age at sea level and includes children with pulmonary vascular resistance (PVR) ≥ 3 WU[4,7]. PH is classified into 5 groups on the basis of each category sharing similar hemodynamics, pathological findings as well as similar management strategies: pulmonary arterial hypertension (PAH; group 1), PH due to left heart disease (group 2), PH due to lung disease and/or hypoxia (group 3), chronic thromboembolic PH (group 4) and PH with unclear/multifactorial mechanisms (group 5)[8].

The risk factors associated with the development of PH in DS are multifactorial. Chromosomal abnormalities such as trisomy 21 have been attributed to an increased risk of developing PH with an odds ratio of 36 (95%CI: 4.15-312.24), implying a genetic contribution to PH development using univariate logistic regression[9]. The presence of congenital heart disease (CHD) is a major contributing factor to PH in the DS population. Other risk factors include defects in lung development (due to overexpression of anti-angiogenesis genes on chromosome 21)[10], pulmonary hypoplasia [11], endothelial dysfunction[12,13], pulmonary diseases[14-18], gastrointestinal diseases[19] and endocrine abnormalities[20]. At the molecular level, it has been proposed

that increased gene dosage of four interferon receptors encoded on chromosome 21 results in increased interferon activation which may contribute to various disease processes in DS[21]. In addition, high interferon gamma levels have also been observed in pulmonary hypertension and are believed to be responsible for pulmonary vascular remodeling[22]. This probable relationship, however, requires further study.

Herein, we describe the first systematic review and meta-analysis which consolidates our existing knowledge on the prevalence of PH in DS. Our objective was to establish the prevalence of PH in children with DS. This systematic review also aims to provide sufficient evidence which could guide policy-making aimed at the prevention and effective management of PH as well as underpin further research.

MATERIALS AND METHODS

Meta-analysis of observational studies in epidemiology (MOOSE) guidelines were followed for this systematic review[23]. The protocol for this systematic review and meta-analysis was registered at the International Prospective Register of Systematic Reviews (PROSPERO # CRD42020204914).

Search strategy

A two-stage search strategy was used for this study.

Bibliographic database search

Electronic databases (PubMed, Cochrane library, EMBASE, Scopus, Web of Science) were searched. The search was restricted by English language with published studies including human subjects only, but not restricted by date or publication types. Studies with insufficient data such as abstracts only, studies with adult participants, conference papers and duplicate publications were excluded. Studies whose data could not be accessed even after a request from the authors were also excluded. The process of data extraction and quality control was performed independently by two reviewers (DP and PZJ). In the event of a conflict, a third reviewer's (AT) opinion was sought. The last electronic search was carried out on 30th June, 2020. The search strategy included the following: ("hypertension, pulmonary"[MeSH Terms] OR ("hypertension"[All Fields] AND "pulmonary"[All Fields]) OR "pulmonary hypertension"[All Fields] OR ("pulmonary"[All Fields] AND "hypertension"[All Fields])) AND ("down syndrome"[MeSH Terms] OR ("down"[All Fields] AND "syndrome"[All Fields]) OR "down syndrome"[All Fields] OR ("downs"[All Fields] AND "syndrome"[All Fields]) OR "downs syndrome"[All Fields]) AND prevalence.

Searching other sources

An individual manual search was also performed which included examining the references of all the eligible papers and other related review articles as well as recent conference proceedings or recommendations on PH. Additional studies from these sources were then included in the review, provided they fulfilled the inclusion criteria.

All studies were handled by the literature management software Endnote X7. This was carried out to ensure no duplication. A preliminary screening of studies was performed by 2 independent authors (AT and PZJ). Screening of all titles and abstracts was done, and the full text was studied for any article considered relevant. After the initial round of screening, sorting was carried out again by re-reading all the articles. Methods were adapted as per PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines for meta-analyses[24].

Eligibility criteria for studies

Any observational study which determined the prevalence of PH in DS was considered for the analysis. These studies needed to mention the number of patients with PH and the number of children with DS who had PH.

Inclusion criteria

(1) All cross-sectional, case–control or cohort studies including children with DS reporting the prevalence of PH; (2) Studies must use either right heart catheterization for diagnosis with the cut-off being mPAP ≥ 25 mmHg or a 2D echocardiogram for determination of pulmonary arterial systolic pressure (PASP) (> 25 mmHg); and (3) All published studies from 1st January 1980 to 30th June 2020 were included.

Exclusion criteria

(1) Studies performed in non-human subjects; (2) Case series, reviews, letters, commentaries and editorials; (3) Studies with insufficient data, abstracts, adult studies, conference abstracts and duplicate publications; and (4) Studies whose key data were not accessible even after a request from the authors.

Selection of studies

Two investigators (PZJ and DP) separately reviewed articles and screened them for eligibility. Full texts were downloaded for any articles which were deemed eligible. The investigators also checked the full texts of each study and studies which met the inclusion criteria were included. A third author (AT) was consulted to resolve any disagreements. A screening test was used to ensure that all review authors reliably applied the selection criteria. Agreement was measured using the kappa (κ) statistic [25].

Data extraction and management

A standard data extraction form was used to retrieve relevant information. Two review authors (PZJ and DP) participated in data extraction independently. PZJ and DP extracted data which included general information (authors, year, and country), study design, diagnostic criteria for PH, and prevalence of PH. In studies where only preliminary data were provided, such as sample size or number of outcomes, other required data were calculated based on these values. Data were extricated using a preconceived and standardized data abstraction form. Studies with un-interpretable data were excluded from the analysis. Level of agreement was ascertained by the κ statistic[25].

Quality appraisal of the studies included

Each included study was evaluated for quality of methodology and risk of bias by two investigators (PZJ and DP) using an adapted version of the Risk of Bias Tool for Prevalence Studies developed by Hoy *et al*[26]. The STROBE checklist[27] was utilized to assess the reporting quality of each study. Reporting of Observational Studies in Epidemiology (STROBE) was performed by two authors. The STROBE statement has a total of 22 items on the checklist. These items relate to various parts of the study such as the article's title and abstract (item 1), the introduction (items 2 and 3), methods (items 4–12), results (items 13–17) and discussion sections (items 18–21), and other information (item 22 on funding). Agreement was measured using the κ statistic[25].

Statistical analysis

Each included study reported the prevalence of pulmonary hypertension as a probability of binominal distribution. Forest plot was used to determine the combined prevalence from the studies and extent of heterogeneity between them. As there was a large difference in the clinical data of patients across the studies, a random-effects meta-analysis was used to pool the data on prevalence[28], after stabilizing the variance of individual studies utilizing the Freeman-Tukey double arc-sine transformation[29]. Heterogeneity of the included studies was tested by Cochran's *Q* test and I^2 index[30]. The degree of heterogeneity was categorized into 3 categories under the I^2 index: heterogeneity lower than 25%, heterogeneity between 25% and 75% and heterogeneity more than 75%. While combining the prevalence of PH, a random effects model was used due to the wide heterogeneity among the studies. The impact of each study was also evaluated by sensitivity analysis. Subgroup analysis of PH was carried out to ascertain the cause of heterogeneity. Sub-group analysis was performed on the basis of geographical distribution (Asia *vs* non-Asia), age, sex, etiology, quality of the studies, year of publication and diagnostic methods. Meta-regression model (method of moments) was performed on the basis of the year of publication of studies[31]. Publication bias was identified by Egger and Begg's tests. Data were analyzed using Comprehensive Meta-Analysis Software Version 2 and values lower than 0.05 were considered to be significant. High-resolution forest plots, with random effects, were separately created[32].

RESULTS

Characteristics of the included studies

Initially, a total of 1578 articles were identified (Figure 1). After elimination of dup-

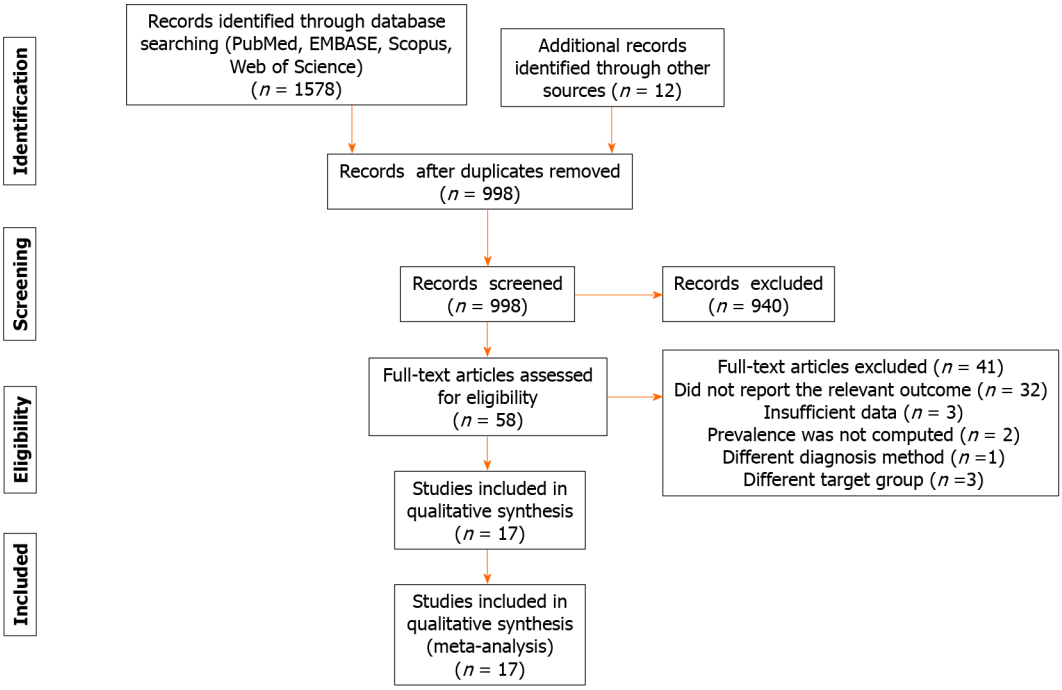

Figure 1 PRISMA flow chart diagram describing the process of identification and selection of studies for inclusion in the review.

licates, screening titles and abstracts, 940 papers were found to be completely irrelevant and excluded. Agreement between investigators on abstract selection was high ($\kappa = 0.90$, $P < 0.001$). Full texts of the remaining 58 studies were scrutinized for eligibility, among which 41 studies were excluded for various reasons. The investigators were in complete agreement for full text selection. Overall, seventeen studies were included for review in the meta-analysis (Figure 1).

All 17 studies noted the prevalence of PH without any analysis and no study reported the incidence of PH. The studies included were published from 2003 to 2020. Ten studies collected data retrospectively and seven studies collected the data prospectively. Study characteristics are summarized in Tables 1 and 2. The age of the patients ranged from neonate to 21 years. The studies differed in sample size varying from 35 to 1252 subjects with a summated sample size of 5393.

Quality of studies

The quality assessment results are presented in Table 3. No study met all criteria of the quality assessment score. Study quality varied from 10 to 17 as per the STROBE criteria. A score of < 14 was considered low quality, and > 14 was considered good/fair quality. The quality of reporting was low for two studies[33,34] and was good/fair for the remaining 15 studies. The most common limitations faced during STROBE assessment were inability to gauge the required sample size and poor projection of the results to the general population.

Risk of bias and heterogeneity

Quality assessment was also conducted for each study using the risk of bias assessment tool[26]. Among the 17 included studies (Table 4), there was low risk of bias for six studies (35.30%)[34-39], moderate risk for eight studies (47.05%)[40-47] and high risk for three studies (17.652%)[6,33,48]. Investigators' agreement on quality assessment of studies was high ($\kappa = 0.88$, $P < 0.001$). High heterogeneity was seen amongst the included studies according to Cochrane Q test (Q test; $P = 0.00001$) and I^2 test (98.4%).

Prevalence of pulmonary hypertension in DS children

Prior studies have estimated the prevalence of PH in children with DS to be as high as 6% and 15% at 1 and 10 years of life, respectively, but data from large populations are lacking[44]. A wide disparity was seen among the various studies for PH prevalence. The heterogeneity was high ($I^2 = 97.20\%$, $P < 0.001$). The overall prevalence of the meta-analysis of 17 studies, according to the Der Simonian-Laird random-effects model, revealed that the pooled prevalence of PH among children with DS was 25.5%

Table 1 Characteristics of studies included in the meta-analysis

Ref.	Year	Timing of data collection	Study design	Country	Population size	Cases with PH	Prevalence of PH
De Rubens *et al*[48]	2003	Retrospective	Observational	Mexico	275	41	14.90909
Shah *et al*[33]	2004	Retrospective	Observational	Canada	175	24	13.71429
Cua *et al*[35]	2007	Retrospective	Observational	USA	58	7	12.06897
Weijerman *et al*[40]	2010	Prospective	Cohort	Netherlands	820	25	3.04878
Banjar *et al*[41]	2012	Retrospective	Observational	Saudi Arabia	59	44	74.57
Mourato *et al*[42]	2013	Retrospective	Cross-sectional	Brazil	138	42	30.43478
Sharma *et al*[43]	2013	Prospective	Observational	India	35	18	51.42857
Shrestha *et al*[36]	2013	Prospective	Observational	Nepal	50	21	42
Espinola-Zavaleta *et al*[44]	2015	Prospective	Observational	Mexico city	127	102	80.31496
Bermudez *et al*[34]	2015	Retrospective	Observational	Brazil	1207	57	4.722452
Zonouzi *et al*[45]	2015	Prospective	Cross-sectional	Iran	110	23	20.90909
Joffre *et al*[6]	2016	Retrospective	Observational	France	66	19	28.78788
Okeniyi *et al*[37]	2017	Prospective	Observational	Nigeria	70	14	20
Bush *et al*[38]	2018	Retrospective	Cohort	USA	1252	346	27.63578
Martin *et al*[39]	2018	Retrospective	Cohort	Ireland	121	41	33.8843
Zahari *et al*[46]	2019	Retrospective	Cohort	Malaysia	754	160	21.22016
Alsuwayfee *et al*[47]	2020	Prospective	Cross-sectional	Iraq	76	23	30.26

PH: Pulmonary hypertension.

(95%CI: 17.4%–35.8%). The forest plot is shown in Figure 2.

Stability of the meta-analysis was assessed by sensitivity analysis. The observations remained largely the same. This similarity between the results showed the stability of our meta-analysis. Also, no significant factor influencing the heterogeneity was identified by the sensitivity analysis.

Subgroup analysis was used to reduce heterogeneity. The pooled prevalence of different subgroups is illustrated in Table 5. There were noteworthy differences for subgroups of gender, age group, region, year of publication, risk of bias and etiology of PH ($P < 0.05$). Four articles[35,38,45,47] presented prevalence linked to gender, with a prevalence of 24.3% among males and 26.2% among females. Some studies reported age distribution while others reported prevalence relating to each age group, which made the results difficult to compare. According to age group, 16 studies were sub-grouped into two categories: studies conducted in infants (less than one year) (4 studies), and studies conducted in infants and children (12 studies). The prevalence of PH among studies including infants and children (33.7%; 95%CI: 22.6%-47%) was higher than studies including only infants (13.4%; 95%CI: 6.6%-25.4%). The prevalence of PH among children with DS from the Asian continent (38.4%; 95%CI: 23.7%-55.7%) was higher than non-Asian continents (19.8%; 95%CI: 10.9%-33.2%). The prevalence of PH was higher in studies published after 2011 (29.8%; 95%CI: 20.2%-41.7%) than those published before 2011 (0.09%; 95%CI: 0.04%-20.0%). Subgroup analyses showed the prevalence of PH among children with DS in studies with moderate risk (34%; 95%CI: 16%-57%) and low risk (20%; 95%CI: 9%-37%) to be higher than studies with high risk of bias (17.8%; 95%CI: 11.6%-26.5%). According to the etiology of PH, 7 studies included were divided into two categories *i.e.* with CHD and without CHD. The prevalence of PH attributable to CHD (14.4%; 95%CI: 7%-26.1%) was higher than in those without CHD etiology (8.9%; 95%CI: 4.4%-17.5%). Only one study, Bush *et al*[38] classified the etiologies as per WHO classification[8]. The diagnosis of PH was made in 82% of children, with 45% being associated with CHD, and 38% having persistent pulmonary hypertension of the newborn (PPHN). The Egger weighted regression statistics ($P = 0.94$) and Begg rank correlation statistics ($P = 0.45$) indicated no evidence of publication bias. There was no sign of publication bias and asymmetry in the funnel plot (Figure 3). The meta-regression model in Figure 4 shows that the prevalence of PH among children with DS has increased in recent years. However, this relationship was

Table 2 Screening methodology of the included studies

Ref.	Diagnosis established by	Age group, (mean ± SD, yr)	Sex (M:F)	Diagnostic criteria for PH
De Rubens *et al*[48]	Echocardiography	Less than 16 yr	1:1	NM
Shah *et al*[33]	Echocardiography	Newborn	10:7	Right to left shunting at ductal or atrial level in the absence of severe pulmonary parenchymal disease
Cua *et al*[35]	Echocardiography	Neonate	25:33	Right-to-left shunt at the ductal level or flattening of the IVS in the absence of a PDA
Weijerman *et al*[40]	Echocardiography	Neonate	NM	Right-to-left shunt at the ductal level
Banjar *et al*[41]	Echocardiography	3.3 ± 3.9	34:25	> 50% of systolic systemic pressure
Mourato *et al*[42]	Echocardiography	Infant	61:77	mPAP > 25 mmHg
Sharma *et al*[43]	Echocardiography	Less than 12 yr	4:3	mPAP >25 mmHg
Shrestha *et al*[36]	Echocardiography	4 mo to 12 yr	1:1.4	NM
Espinola-Zavaleta *et al*[44]	Echocardiography	Up to 18 yr	64:63	mPAP > 30 mm Hg
Bermudez *et al*[34]	Echocardiography	Up to 11 mo	NM	mPAP > 25 mmHg
Zonouzi *et al*[45]	Echocardiography	1 mo-20 yr	53:57	NM
Joffre *et al*[6]	Echocardiography	1mo-16 yr	2:1	NM
Okeniyi *et al*[37]	Echocardiography	3 mo-9 yr	3:4	NM
Bush *et al*[38]	Echo or catheterization	Birth to 21 yr	688:564	mPAP > 25 mmHg; IVS flattening, RV dilation, or presence of RV hypertrophy
Martin *et al*[39]	Echocardiography	Neonate	62:59	Right to-left shunt across the PDA, IVS bowing into the left ventricle, or the presence of a TR jet
Zahari *et al*[46]	Echocardiography	Newborn	189:225	IVS flattening, a dilated main pulmonary artery, and dilated right cardiac chambers
Alsuwayfee *et al*[47]	Echocardiography	< 15 yr	0.85:1	mPAP > 25 mmHg

PH: Pulmonary hypertension; IVS: Interventricular septum; PDA: Patent ductus arteriosus; TR: Tricuspid regurgitation; PAP: Pulmonary artery pressure; NM: Not mentioned.

not statistically significant (meta-regression coefficient: 0.0947, 95%CI: -0.035 to 0.22, P = 0.153).

DISCUSSION

Children with DS are known to be at a higher risk of developing pulmonary hypertension (PH). This can be attributed to underlying CHDs, idiopathic PH and partly due to upper airway obstruction[49]. Other factors which may contribute to a higher risk include genetics, anatomical characteristics of the pulmonary vasculature, pulmonary hypoplasia, obstructive airway diseases, chronic infection and neuromuscular underdevelopment. Increased pulmonary blood flow due to underlying heart disease with left to right shunt increases the sheer stress on the endothelial lining and may induce endothelial dysfunction, eventually resulting in pulmonary vasculature remodeling. The sheer stress also leads to pathologic changes in the vessel wall such as endothelial cell proliferation and thickening of the vessel wall. The pathologic changes also include alveolar under-development. The production of prostacyclin and nitric oxide is diminished in DS, but endothelin-1 and thromboxane are elevated[50]. The lifetime incidence of PH in children with DS remains unknown [38]. Patients with DS have increased mortality due to pulmonary vascular disease with a standardized mortality odds ratio of 3.83 (95%CI: 3.60-4.07)[51].

In light of this, this is the first systematic review evaluating PH in children with DS. Despite extensive literature, there is large heterogeneity in the prevalence of PH in DS. The heterogeneity arises from multiple overlapping etiologies which are commonly associated with DS. The present study found the overall prevalence to be 25.5%

Table 3 Quality assessment of the included studies

STROBE quality of reporting						
Ref.	The title and abstract (Item 1)	Introduction (Item 2-3)	Methods (Item 4-12)	Results (Item 13-17)	Discussion and other information (Item 18-22)	Quality score (0-22)
De Rubens *et al*[48]	1	2	6	4	2	15
Shah *et al*[33]	0	2	5	2	3	12
Cua *et al*[35]	1	2	5	3	4	15
Weijerman *et al*[40]	1	2	4	4	4	15
Banjar *et al*[41]	1	2	4	4	4	15
Mourato *et al*[42]	1	2	5	2	4	14
Sharma *et al*[43]	1	2	5	3	4	15
Shrestha *et al*[36]	1	2	4	4	4	15
Espinola-Zavaleta *et al*[44]	1	2	5	3	3	14
Bermudez *et al*[34]	1	2	4	2	4	13
Zonouzi *et al*[45]	1	2	4	3	5	15
Joffre *et al*[6]	1	2	5	2	4	14
Okeniyi *et al*[37]	1	2	5	3	3	14
Bush *et al*[38]	1	2	5	3	5	16
Martin *et al*[39]	1	2	5	4	4	16
Zahari *et al*[46]	1	2	5	3	4	15
Alsuwayfee *et al* [47]	1	2	5	4	4	16

(95%CI: 17.4%-35.8%) from a pool of 17 studies which met the inclusion criteria. This finding has shown concordance with multiple studies[6,37,38,45,46]. In order to reduce heterogeneity, subgroup analysis was carried out according to age, gender, region, etiology of PH and bias. In neonates, the incidence of PH is estimated at 2 per 1000 live births, which is notably less when compared to that observed in neonates with DS[52]. Earlier studies assessing PH in children with DS report an incidence ranging from 1% to 5%, with the majority of these infants being classified as having pulmonary arterial hypertension (PAH). More recent studies, however, have noted a much higher figure ranging between 27% and 34%[38]. Additionally, children with DS have an increased risk of developing PPHN even in the absence of structural heart disease and should be followed up until resolution of PH[33].

According to age group, 16 of the included studies were divided into 2 subgroups: studies conducted in children < 1 year of age (7 studies) and studies conducted in children > 1 year of age (9 studies). The prevalence of PH in DS was highest in children followed by infants and neonates. This contrast was highlighted because of the identification that infants with DS have a higher prevalence of PPHN and abnormalities of developmental lung disorders (*e.g.*, reduced alveolarization, decreased vessel density, persistence of the double-capillary network and hypertensive arterial remodeling). This finding enforces that increasing age is a distinct risk factor for developing PH and its complications. Late PH is also important in contributing to adverse outcomes in children and adults with DS[38]. In the current review, 4 studies analyzed the prevalence of PH according to gender. The overall prevalence in females was 26.2% and in males it was 24.3%. Although, the prevalence was higher in females the difference was not statistically significant. When country of origin was considered in the analysis, it was noted that Asian countries showed a higher prevalence as compared to non-Asian countries (38.4% *vs* 19.8%). Studies published before 2011 recorded a pooled prevalence of only 9.4%, whereas after 2011 the prevalence was found to be 33%. This increased prevalence can be attributed to reasons such as increased survival of children with DS and CHD and increased birth rates. In a study conducted by Yang *et al*[51], among 17,897 patients with DS, the median age at death had increased from 25 years in 1983 to 49 years in 1997. A large percentage of PH in DS

Table 4 Risk of bias assessment of included studies using the Hoy *et al*[26] 2012 tool

Ref.	Representation	Sampling	Random selection	Non response bias	Data collection	Case definition	Reliability and validity of study tool	Method of data collection	Prevalence period	Numerator and denominator	Summary assessment
De Rubens *et al*[48]	HR	HR	HR	HR	HR	HR	LR	LR	HR	LR	HR
Shah *et al*[33]	HR	HR	HR	HR	HR	HR	LR	LR	HR	LR	HR
Cua *et al*[35]	LR	LR	LR	LR	LR	LR	LR	LR	HR	LR	LR
Weijerman *et al*[40]	HR	HR	HR	HR	HR	LR	LR	LR	HR	LR	MR
Banjar *et al*[41]	HR	HR	LR	HR	LR	HR	LR	LR	LR	LR	MR
Mourato *et al*[42]	HR	HR	HR	HR	LR	LR	LR	LR	HR	LR	MR
Sharma *et al*[43]	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR	LR
Shrestha *et al*[36]	LR	LR	LR	HR	LR	LR	LR	LR	HR	LR	LR
Espinola-Zavaleta *et al*[44]	LR	LR	LR	HR	HR	HR	LR	LR	HR	LR	MR
Bermudez *et al*[34]	LR	LR	HR	HR	LR	HR	LR	LR	HR	LR	MR
Zonouzi *et al*[45]	HR	HR	HR	HR	LR	HR	LR	LR	HR	LR	MR
Joffre *et al*[6]	HR	HR	HR	HR	HR	HR	HR	HR	LR	LR	HR
Okeniyi *et al*[37]	LR	LR	LR	HR	HR	LR	LR	LR	HR	LR	LR
Bush *et al*[38]	LR	LR	LR	HR	HR	LR	LR	LR	HR	LR	LR
Martin *et al*[39]	LR	LR	LR	HR	HR	LR	LR	LR	HR	LR	LR
Zahari *et al*[46]	HR	LR	HR	HR	LR	HR	LR	LR	HR	LR	MR
Alsuwayee *et al*[47]	HR	HR	HR	HR	LR	LR	LR	LR	LR	LR	MR

HR: High risk; LR: Low risk; MR: Moderate risk (LR: 0-3; MR: 4-6; HR: 7-9).

can be attributed to the concomitant presence of CHDs. Laursen *et al*[53] in 1976, found that the incidence of PH in patients with DS and CHDs to be just 2%, whereas a study conducted by Bush *et al*[38] in 2018 found the incidence of PH in DS to be as high as 28%. The incidence was noted to increase to 45% in the presence of a co-morbid CHD. They also noted that the higher age group in their study may be responsible for the higher incidence.

The risk of bias was high in 3 studies with the prevalence of PH being 17.8%, 6 studies had low risk of bias with a prevalence of 20% and 8 studies with moderate risk showed a prevalence of 34%. There were 7 studies which assessed the prevalence of PH in children with DS with an underlying CHD. These studies had a prevalence of 14.4% while studies having no underlying CHD (7 studies) had a prevalence of 8.9%. Patients with an underlying CHD showed a higher prevalence of PH. Other studies have observed similar findings. Smith *et al*[54] reported that DS patients had a higher prevalence of PH with or without an underlying CHD and the difference between the

Table 5 Prevalence in different subgroups

Stratification group	Number of studies	Total number of subjects	Total number of events	I^2	*P* value	Prevalence	95%CI
Sex							
Male	4	801	210	28.22	0.243	24.3	18.8-30.6
Female	4	695	189	56.44	0.076	26.2	18.8-35.3
Age							
Infant (< 1 yr)	7	3273	356	95.35	0.000	13.4	6.6-25.4
Children (> 1 yr)	9	2061	607	94.68	0.000	33.7	22.6-47.0
Region							
Asia	6	1084	289	93.68	0.000	38.4	23.7-55.7
Not Asia	11	4309	718	97.92	0.000	19.8	10.9-33.2
Studies published							
Before 2011	4	1328	97	93.79	0.000	9.4	4.1-20.2
2011 - 2020	13	4065	910	97.13	0.000	33.0	22.5-45.4
Risk of bias							
High risk	3	516	84	76.20	0.015	17.8	11.6-26.5
Moderate risk	8	2119	437	97.91	0.000	34.0	16.6-57.1
Low risk	6	2758	486	97.63	0.000	20.0	9.3-37.7
Etiology							
Cardiac	7	724	372	97.06	0.000	14.4	7.4-26.1
Non-cardiac	7	724	352	96.63	0.000	8.9	4.4-17.5

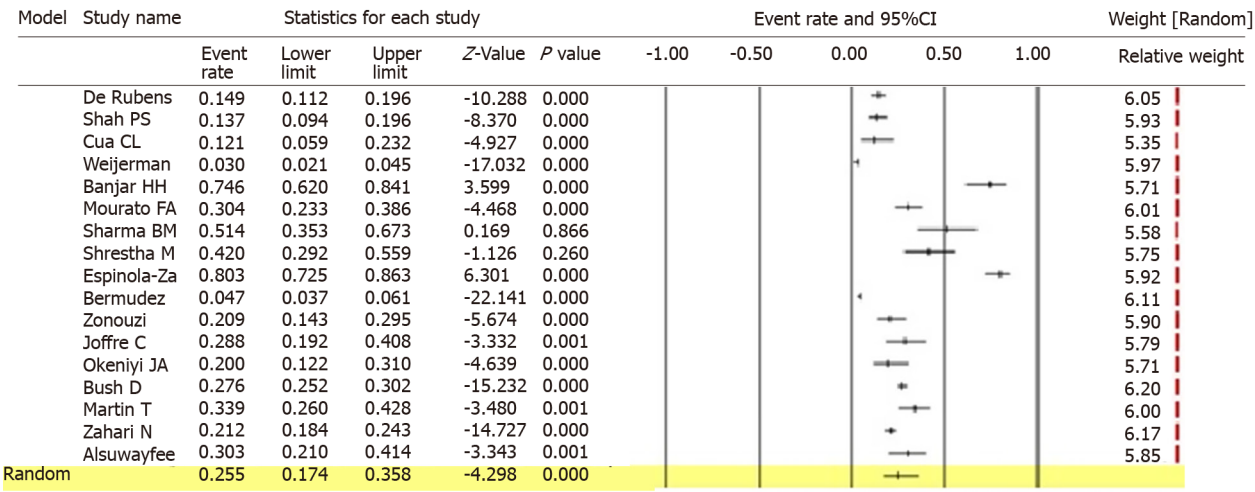

Figure 2 Forest plots of pulmonary hypertension prevalence among children with Down syndrome.

two groups lies in the underlying etiology and the age of presentation. Iwaya *et al*[55] reported a lower pulmonary arterial compliance in individuals with CHD in DS when compared to CHD without DS. A noteworthy association was found between low pre-operative pulmonary compliance in DS and the need for postoperative oxygen therapy after discharge.

Study strengths and limitations

This is the only systematic review and meta-analysis assessing the prevalence of PH in the pediatric population with DS. A comprehensive search was undertaken wherein we included any study that reported the prevalence of PH in children with DS. Despite considerable heterogeneity between studies, our review provides the most

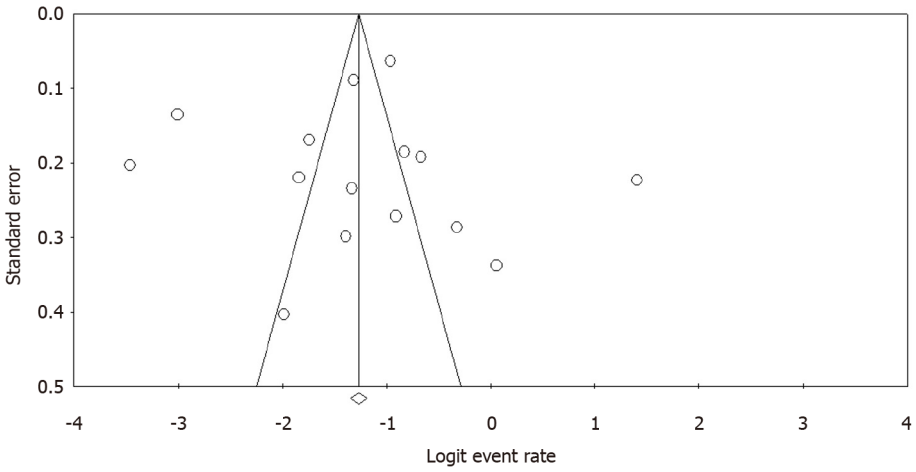

Figure 3 Funnel plots of pulmonary hypertension prevalence among children with Down syndrome.

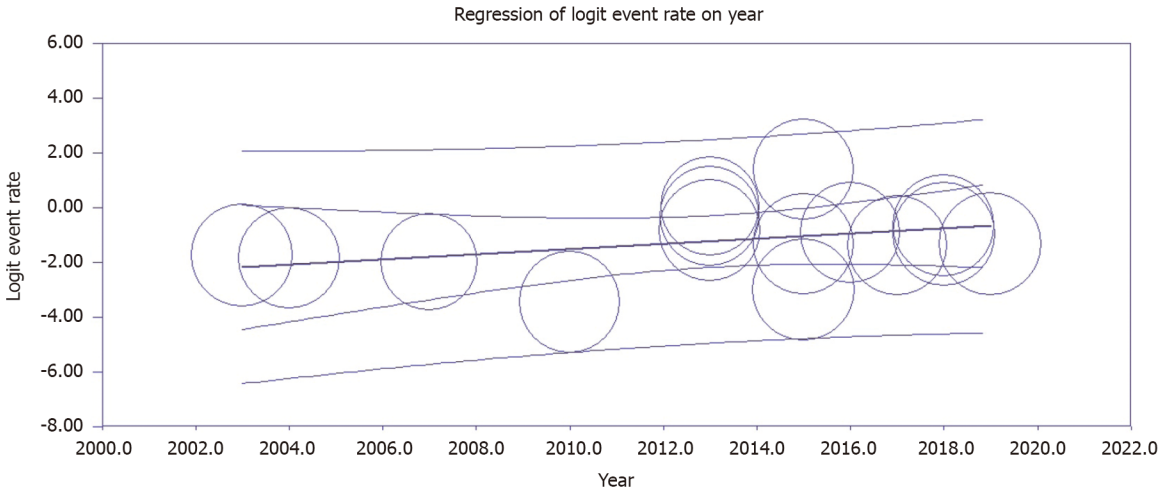

Figure 4 Meta-regression of pulmonary hypertension prevalence based on the year of the study.

comprehensive estimate of PH prevalence in children with DS to date, and most importantly, allows the comparison of prevalence between various groups of interest. Heterogeneity may arise from the data sources, populations examined and subjects with different ages, sex, risk of bias *etc*. This is not unexpected in view of the different populations studied and the nature of variations associated with the different methods used in estimating the prevalence. However, the sensitivity analysis showed that the heterogeneity had no significant impact on the pooled prevalence and a meta-analysis might still provide insights on the overall prevalence. The quality of the results and risk of bias of the studies included was at most, moderate, further highlighting that further such research may have a significant impact on our confidence in the estimate and might also change it. All included studies were observational; therefore, a cause effect relationship cannot be concluded between PH in children with DS. Longitudinal and interventional studies are still needed to determine the nature of any cause and effect relationship. Finally, some methodological limitations of the current meta-analysis were inevitable and should be taken into consideration while interpreting the results. Our study, although strengthened by rigid quality assessment, was limited by the fact that not all studies had classified all the etiologies of PH as per the WHO classification. The paucity of etiological data made it difficult to delineate individual causes of PH in patients with DS. This added to existing heterogeneity while analyzing the exact prevalence of PH in DS. More studies, specifically, ones with community screening for PH in DS are required to come to an exact estimate.

CONCLUSION

This article highlights the increasing prevalence of PH in children with DS. In order to improve the care given and reduce the disease burden, the attending pediatrician has a crucial role in being aware of this morbid disease and to channel his/her efforts towards routine screening of PH, earlier diagnosis and successful management. In addition, there should be early routine echocardiographic screening in children with DS even in the absence of CHDs. Community-based studies with a larger sample size of children with DS may be carried out to better characterize the epidemiology and underlying etiology. Our study reinforces what is already known and provides, in addition, reliable information about the prevalence of PH in DS.

ARTICLE HIGHLIGHTS

Research background

Children with Down syndrome (DS) have an increased likelihood of developing pulmonary hypertension (PH) with serious short- and long-term consequences. Approximately 75% of all deaths in DS may be attributed to pneumonia and infectious lung disease, congenital heart disease (CHD) and circulatory disease (vascular diseases such PH). Despite the overwhelming evidence of morbidity, there have been no studies estimating the precise disease burden of PH in children with DS.

Research motivation

Additional information is required to collate the prevalence rates of PH in order to undertake definitive measures for early diagnosis and management.

Research objectives

The objective of this study is to determine the prevalence of PH in children with DS.

Research methods

The electronic databases (PubMed, Cochrane library, EMBASE, Scopus, Web of Science) were searched. Any observational study which determined the prevalence of PH in DS was considered for the analysis. Data were extricated using a preconceived and standardized data abstraction form. The data were analyzed by Comprehensive Meta-Analysis Software Version 2.

Research results

Of 1578 articles identified, 17 were selected for final analysis. The pooled prevalence of PH in these studies was 25.5% (95%CI: 17.4%–35.8%). Subgroup analysis was carried out for age, gender, region, year of publication, risk of bias and etiology of PH.

Research conclusions

This article highlights the increasing prevalence of PH in children with DS. This is accounted for by the high prevalence of underlying CHDs in these children. In order to improve the care given and reduce the disease burden, the attending pediatrician has a crucial role in being aware of this morbid disease and to channel his/her efforts towards routine screening of PH, earlier diagnosis and successful management. In addition, there should be early routine echocardiographic screening in children with DS even in the absence of CHDs. Community-based studies with a larger sample size of children with DS may be carried out to better characterize the epidemiology and underlying etiology of PH in DS. Our study reinforces what is already known and provides, in addition, reliable information about the prevalence of PH in DS.

Research perspectives

Further studies are required to better characterize the epidemiology, underlying etiology, pathogenesis and risk factors of PH in children with DS.

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World Journal of Clinical Pediatrics

Submit a Manuscript: https://www.f6publishing.com

World J Clin Pediatr 2021 November 9; 10(6): 192-199

DOI: 10.5409/wjcp.v10.i6.192

ISSN 2219-2808 (online)

CASE REPORT

Treatment of alopecia totalis/universalis/focalis with vitamin D and analogs: Three case reports and a literature review

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Author contributions: Papadimitriou DT was the patient's treating pediatric endocrinologist and contributed to the drafting and editing of the manuscript; Bothou C reviewed the literature and contributed to drafting the manuscript; Dermitzaki E performed the clinical follow-up; Alexopoulos A performed the dermatological evaluations; Mastorakos G reviewed and supervised the manuscript drafting and interpreted the clinical implications; All authors issued final approval for the version to be submitted.

Informed consent statement: Informed written consent was obtained from the patients' guardians for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE

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Abstract

BACKGROUND

Alopecia areata (AA) is an inflammatory disease with autoimmune, environmental, and inherited components directed at the hair follicle, either limited to patchy hair loss over the scalp (Focalis, AF), total loss of scalp hair (Totalis, AT), or total loss of both scalp and body hair (Universalis, AU). Despite multiple treatment modalities, no therapy exists. Vitamin D deficiency in patients with AA/AT/AF influences disease severity and duration, inversely correlating with inflammation histologically.

CASE SUMMARY

Three girls presented with AT (P1), AU (P2), and AF (P3) at the ages of 1, 5, and 5 years, respectively. For P1-P2, all available treatments implemented for 2 years had failed. We started an initial 6-mo repletion with oral cholecalciferol 2000/4000 IU/d, with no apparent effect. Then we attempted immunomodulation using oral calcitriol and its analog paricalcitol. On calcitriol, 0.5 mcg/d P1 regrew hair within 6 mo. After 4 years, a relapse with loss of eyebrow hair was resolved after doubling the calcitriol dose to 0.5 mcg × 2/d; the results have been maintained for 6 years to date. On calcitriol, 0.25 mcg × 3/d P2 led to the development of asymptomatic hypercalcemia-hypercalciuria, which was immediately resolved by

Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Specialty type: Endocrinology and metabolism

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: November 11, 2020
Peer-review started: November 11, 2020
First decision: April 6, 2021
Revised: April 18, 2021
Accepted: July 6, 2021
Article in press: July 6, 2021
Published online: November 9, 2021

P-Reviewer: Sideris N
S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Yuan YY

switching to paricalcitol 2 mcg × 3/d; mild tolerable hypercalciuria was maintained. Hair regrowth was observed at 6 mo, stabilizing only as fur at 12 mo. AF in P3 was resolved completely within 3 mo on a daily high dose (8000 IU) of cholecalciferol.

CONCLUSION

Vitamin D may have immunomodulating therapeutic impact on AT/AU/AF, which needs to be explored with further pilot clinical trials.

Key Words: Alopecia totalis; Alopecia universalis; Alopecia focalis; Calcitriol; Paricalcitol; Vitamin D; Case report

Core Tip: Alopecia areata (AA) is an inflammatory disease with autoimmune, environmental, and inherited components directed at the hair follicle, either limited to patchy hair loss over the scalp (Focalis, AF), total loss of scalp hair (Totalis, AT), or total loss of both scalp and body hair (Universalis, AU). Despite multiple treatment modalities, there is no current therapy. Three girls aged 3, 7, and 5 years with AT, AU, and AF were treated with oral calcitriol, paricalcitol, and cholecalciferol, showing hair regrowth at 6, 6, and 3 mo, respectively but only as fur for P2 with AU. Vitamin D may have an immunomodulating therapeutic impact on AT/AU/AF, which needs to be explored with further pilot clinical trials testing the effectiveness and establishing the optimal form and dosage of vitamin D.

Citation: Papadimitriou DT, Bothou C, Dermitzaki E, Alexopoulos A, Mastorakos G. Treatment of alopecia totalis/universalis/focalis with vitamin D and analogs: Three case reports and a literature review. *World J Clin Pediatr* 2021; 10(6): 192-199
URL: https://www.wjgnet.com/2219-2808/full/v10/i6/192.htm
DOI: https://dx.doi.org/10.5409/wjcp.v10.i6.192

INTRODUCTION

Alopecia areata (AA) is a non-scarring T-cell mediated autoimmune disease directed at the hair follicle (HF), either limited to patchy hair loss over the scalp (Focalis, AF), total loss of scalp hair (Totalis, AT), or loss of both scalp and body hair (Universalis, AU). Its prevalence among the young and adult population is 0.7%-3.8%, significantly affecting patients' lives and having psychosocial implications. Management of the disease can be challenging, and despite multiple treatment modalities, no successful treatment is available. Pediatric age and more extensive disease with resistance to initial therapies with corticosteroids may sometimes benefit from a cocktail of established therapies. The likelihood of complete spontaneous regrowth in AA is estimated to be less than 10%, but even then, relapses are common and frustrating[1].

HF is a micro-organ with its own immune and hormonal microenvironment. During the anagen segment of the hair cycle, HF epithelium generates and maintains an area of immune privilege, which is mainly characterized by the low expression of major histocompatibility complex class Ia antigens and local production of immunosuppressive agents. This HF immune privilege (HFIP) is important for the protection of anagen- and melanogenesis-associated antigens from immune recognition by autoreactive CD8+ T cells. The collapse of mechanisms that maintain the HFIP renders the HF susceptible to inflammatory assault, contributing to the development of AA, while growing evidence implicates interferon gamma in triggering HFIP collapse[2].

The role of vitamin D in the proliferation and differentiation of keratinocytes has been extensively studied and well established in the literature. Vitamin D is synthesized in the epidermal keratinocytes from 7-Dehydrocholesterol by ultraviolet B light (290-315 nm) or is acquired through the diet and dietary supplements[3,4]. Further hydroxylation in the liver leads to 25-hydroxyvitamin-D3 (25OHD3) and subsequently in the kidney to the active hormone 1-25-dihydroxyvitamin-D3 (1-25(OH)2D3, calcitriol). The role of the vitamin D receptor (VDR) in the hair cycle was

first suggested by the observation of alopecia in patients with type II vitamin D dependent rickets (VDDR IIA), an autosomal recessive disorder that, due to a defect in the VDR, is characterized by hypokalemia, hypophosphatemia, hyperparathyroidism, rickets, osteomalacia, dental caries, and alopecia universalis[5]. Patients with VDDR IIA have normal hair at birth, possibly because they have normal HF morphogenesis, but they lose their hair between 1 and 3 mo of age. Histological results of VDDR IIA alopecia include a normal infundibular portion of the HF but the lower two-thirds of the HF, below the level of the sebaceous gland, is replaced by irregular epithelial structures and dermal cysts.

Recent studies in mice and *in vitro* support the pivotal role of VDR in the postnatal maintenance of the HF. In the late anagen and catagen phases, there is an increase in VDR expression, which is associated with the decreased proliferation and increased differentiation of keratinocytes, making the presence of VDR a prerequisite for maintenance of the normal hair cycle[6]. However, the roles of vitamin D and the VDR in the hair cycle have not been completely elucidated, and clinical therapies for hair disorders have not been established. However, vitamin D is an important immunomodulator, and vitamin D deficiency has been reported in many autoimmune diseases [7]. Recent retrospective studies among AA patients compared to controls reveal significantly reduced vitamin D levels among patients[8,9].

We present three cases with AT/AU/AF that emphasize the pivotal role of treatment with cholecalciferol, the active hormone calcitriol, and its analogue paricalcitol.

CASE PRESENTATION

Chief complaints

Sudden and total hair loss in the scalp, both the scalp and body, and in multiple focalized areas of the scalp in three girls aged 1, 5, and 5 years, respectively.

History of present illness

Two girls diagnosed with AT and AU based on clinical examination[10], who experienced sudden (within 3 mo) and total hair loss at the age of 1 and 5 years, presented to our pediatric endocrine unit at the ages of 3 (patient #1, P1) and 7 years (patient #2, P2), respectively. For 2 years, all available local and systemic treatments including oral methotrexate had been tried by pediatric and adult dermatology clinics with no results.

A third girl aged 5 years (patient #3, P3) presented with sudden (within the last month) hair loss compatible with AF.

History of past illness

None of the patients were suffering from other chronic dermatological diseases (vitiligo and psoriasis) or other systemic diseases such as diabetes mellitus, anemia, hypothyroidism or hyperthyroidism, systemic lupus, rheumatoid arthritis, chronic renal or liver disease, also autoimmune polyendocrinopathy type 1 was also excluded with the necessary laboratory testing. In P3, although there was normal thyroid function with negative anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Tg) antibodies, signs of Hashimoto's thyroiditis were shown in thyroid ultrasonography (U/S) performed by a pediatric radiologist. All three girls were vitamin D-deficient with vitamin D levels (25OHD3) of 60 nmol/L (24 ng/mL) in P1, 50 nmol/L (20 ng/mL) in P2, and 42.5 nmol/L (17 ng/mL) in P3, and normal calcium metabolism and parathyroid hormone (PTH) (PTH < 45 ng/mL)[11]. Zinc, B12, vitamin A, vitamin E, and ferritin levels were within normal range in all patients, also with negative celiac serology.

Personal and family history

None of the patients nor any first-degree family members were suffering from other chronic dermatological diseases (vitiligo and psoriasis).

Physical examination

In P1, there was complete absence of scalp hair and eyebrows. In P2, there was complete absence of body hair. In P3, five localized areas had complete hair loss at the scalp, with a diameter of 3-5 cm, along with a palpable goiter (Figure 1). An experienced pediatric dermatologist found no apparent focal or systemic dermatological

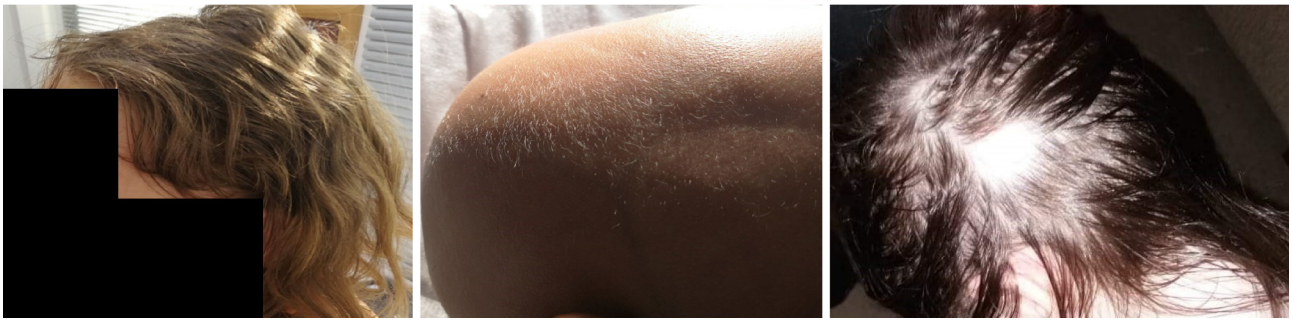

Figure 1 Hair regrowth in the alopecia totalis case (P1, top) and the alopecia universalis case (P2, middle); and presentation of the alopecia focalis case (P3, bottom).

cause in any of the girls, with absence of signs of skin or nail candidiasis, to exclude the possibility of autoimmune polyglandular syndrome.

Laboratory examinations

All three girls were vitamin D-deficient with vitamin D levels (25OHD3) found 60 nmol/L (24 ng/mL) in P1, 50 nmol/L (20 ng/mL) in P2 and 42.5 nmol/L (17 ng/mL) in P3, with the rest of the calcium metabolism and PTH being normal (PTH < 45 ng/mL)[11]. Zinc, vitamin B12, vitamin A, vitamin E, and ferritin levels were within normal range in all patients, also having a negative serology negative for celiac disease.

Imaging examinations

A thyroid ultrasound was performed by a pediatric radiologist. In P3, although there was normal thyroid function with negative anti-TPO and anti-Tg abs, signs of Hashimoto's thyroiditis were found.

FINAL DIAGNOSIS

P1 had AT, P2 AU and P3 AF.

TREATMENT

As P1 and P2 were vitamin D-deficient, we started an initial 6-mo repletion with oral cholecalciferol 2000/4000 IU/d at the upper tolerable daily dose, according to the Endocrine Society Clinical Practice Expert Guideline Committee, *i.e.* infants < 1-year 2000 IU daily and children 1-18 years 4000 IU daily[12] (https://www.endocrine.org/clinical-practice-guidelines/vitamin d deficiency), with no apparent effect on hair growth. Then, based on the previous experience of our group we attempted to induce immunomodulation by oral calcitriol[13-15] in P1 and P2, while both girls were continuously supplemented with cholecalciferol 2000 and 4000 IU p.o., respectively.

Active forms of vitamin D, such as calcitriol (1,25(OH)2 D, the biologically active form of vitamin D), and its up to 10 times less calcemic analog paricalcitol[16], are used to treat secondary hyperparathyroidism occurring in patients with kidney disease, leading to bone disease. Since they have different effects on calcium metabolism, experience in their use as well as special precautions are required (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c3d5546b-ccd4-4988-9d86-9f0b29e12128; https://www.mayoclinic.org/drugs-supplements/paricalcitol-oral-route/precautions/drg-20073059?p=1).

OUTCOME AND FOLLOW-UP

Treatment with 0.5 mcg/d P1 grew hair within the first 6 mo of treatment (except a small region at the rear of the scalp; Figure 1). After 4 years, there was a relapse with loss of eyebrow hair, which was resolved within 3 mo after raising calcitriol dose at 0.5

× 2 mcg/d. The result has been maintained for 7 years now since treatment initiation with normal calcium metabolism: calcium (Ca) 10.1 mg/dL (normal range: 8.5-10.5 mg/dL), phosphorus (P) 5.1 mg/dL (normal range: 3.5-5.5 mg/dL), alkaline phosphatase (ALP) 318 IU/L (normal range: 199-440 U/L), parathyroid hormone (PTH) 26 pg/mL (normal < 45 pg/mL), 25OHD3 41 ng/mL (normal range: 30-150 ng/mL), 1-25 (OH)2D3 30 ng/mL (normal range: 18-80 pg/mL) and normal 0.08 Ca/Cr ratio in a 2 h morning urine sample (normal range: < 0.22).

Treatment with 0.25 mcg × 3/d p.o. P2 developed asymptomatic hypercalcemia – hypercalciuria (Ca 14 mg/dL, Urine Ca/Cr 1.37 in a 2-h morning sample) within 1 mo and was immediately switched to an even higher corresponding dose of paricalcitol [17] at 2 mcg × 3/d p.o. Then calcium metabolism normalized: Ca 9.8 mg/dL, P 3.8 mg/dL, ALP 146 IU/L, PTH 22.4 pg/mL, 25(OH)D 152.5 nmol/L (61 ng/mL), 1-25 (OH)2 D3 38 ng/mL, apart from mild hypercalciuria (Ca/Cr 0.5 in a 2-h morning urine sample), closely monitored and with normal kidney U/S every 6 mo. Hair regrowth including scalp hair, eyebrows and eyelashes was noted by 6 mo but maintained at 12 mo only as fur (Figure 1). With no further improvement, paricalcitol treatment was discontinued at 12 mo with a complete subsequent relapse of AU.

In P3, treatment with high dose cholecalciferol p.o. (8000 IU/d) completely resolved all focalized alopecia areas within 3 mo with normal hair regrowth at all sites and 25(OH)D levels restored at 155 nmol/L (62 ng/mL). At 6 mo dermatological examination of the scalp was completely normal. Cholecalciferol substitution was continued with a maintenance dose of 4000 IU/d, which does not require medical supervision according to the Endocrine Society Expert Committee guidelines, in order to maintain 25(OH)D levels 100-150 nmol/L[12]. Subsequent follow-ups for 2 years were uneventful.

DISCUSSION

We present three cases of AT/AU/AF treated with oral calcitriol, its analogue paricalcitol, and high-dose cholecalciferol. Almost complete hair regrowth including scalp hair and eyebrows was accomplished in the girl with AT on calcitriol treatment. A relapse was avoided by raising the calcitriol dose and the patient can be considered cured, with the result being maintained for 7 years now, having a beneficial effect on the girl's well-being. Treatment with calcitriol is being continued though, as calcium metabolism is completely normal, and the family wishes to maintain it being afraid of a possible relapse. In the AU case, calcitriol caused hypercalcemia – hypercalciuria and was switched to paricalcitol, a less calcemic analog. While hair regrowth was noted by 6 mo of treatment with even eyelashes being temporarily restored, at 12 mo scalp hair was still as fur, leading to treatment discontinuation and subsequent complete AU relapse. In the AF case, early onset high dose daily cholecalciferol treatment was successful, restoring completely alopecia areas with no further relapses. Undoubtedly, just three cases do not suffice to suggest generalized use of the presented approach. Nevertheless, the possible implications of vitamin D in the clinical care of patients with AT/AU/AF, as in autoimmune disorders in general, are being examined and discussed. Using high dose cholecalciferol, calcitriol and paricalcitol, we aimed to exert immunomodulatory effects on T-cells while upregulating the expression of VDR on HF and epidermal keratinocytes. For the safety of the off-label use of calcitriol and paricalcitol we based our approach on the previous experience of our group[13,14] and also on published experience of pediatric patients with chronic kidney disease and hyperparathyroidism[18,19], closely monitoring our patients.

It is well established that vitamin D reduces the function and differentiation of T-helper 17 cells, down-regulates the T-helper 1 cells and increases the action of T-regs, resulting in immunomodulation[7,20]. AT/AU, as an inflammatory disease with autoimmune, environmental, and inherited components, is characterized by imbalance of the above-mentioned parts of the immune system. Previous work of our group has shown the negativation of Type 1 associated autoantibodies after treatment with oral calcitriol[13] but also practically the cure of severe atopic dermatitis, also an autoimmune disease, with calcitriol and its analogue paricalcitol[21] a synthetic analogue with 3 times less binding affinity to the VDR but 10-times less effect on calcium metabolism per se[16].

Regarding the role of vitamin D and its receptor (VDR) in hair, it is well established that VDR is expressed in the outer root sheath (ORS), HF bulb, and the sebaceous gland in the HF and participates in differentiation of HFs[6]. VDR knock out mice (VDR KO) have been proved to suffer from alopecia areata[22]. VDR expression is

decreased in HF and epidermal keratinocytes in AA leading to suppression of Wnt/beta catenin signals and cell differentiation[23]. This downregulation of VDR could be explained either due to the local inflammation that leads to loss of the VDR expression or due to the vitamin D deficiency. This is supported by the hypothesis that vitamin D deficiency is a stimulus for the local inflammation and vice versa, which could lead to a vicious cycle in the chronic status of the disease. Re-appearance of the VDR on HF was detected after topical calcipotriol treatment, a synthetic derivative of calcitriol, used in the treatment of psoriasis[24]. Similarly with other studies presenting small series of patients, using local treatments containing calcipotriol, over 50% experienced improvement of the alopecia manifestations[9,25].

On the other hand, vitamin D deficiency among AA patients is a common finding. Many studies reveal significantly reduced 25(OH)D concentrations among this population[26,27]. Another recent prospective study comparing 30 patients with AA with 30 controls showed that vitamin D deficiency in AA influences disease severity and duration[28]. Simultaneously, VDR expression was reduced in AA and as hypothesized, was inversely correlated with inflammation histologically. These finding suggest, not only the possible relation of vitamin D deficiency with the pathogenesis of the disease but also the potential use of vitamin D as a therapeutic approach. The fact that patients with vitamin D deficiency run a longer course of disease and it takes longer for autoimmunity to regress despite multiple immunosuppressive therapies enhance the hypothesis of a vitamin D role in pathogenesis of AA. Patients with AA have a higher prevalence of vitamin D deficiency and lower 25(OH)D levels than the control groups[29], although further research is needed to elucidate the underlying mechanisms and assess the efficacy of vitamin D in treating AA, as vitamin D may suppress autoimmunity and VDR down regulation.

The study from Daroach *et al*[28] was – to the best of our knowledge – the first effort of systematic supplementation of the vitamin D deficient AA. They used oral cholecalciferol 60.000 IU once weekly for 12 wk and detected clinical improvement and VDR upregulation, even though statistically significant results were not acquired[28]. The reason for this might be that, according to many studies, serum 25(OH)D above a certain cut-off may be required for its immunomodulatory actions but also a minimum duration of treatment for the upregulation of the VDR expression is required[7]. The dosage that has been used in this study would assure normal (30-150 ng/mL) 25(OH)D concentrations, above or around 40-60 ng/mL, as in our AF patient. Though, as in our cases, a pharmacological therapeutic intervention, as the individualized schemes with the active hormone calcitriol and its analog paricalcitol we used, may be required to obtain positive therapeutic results. This is because cholecalciferol is subjected to internal transformation to the active hormone calcitriol to exert most of its' immunomodulatory actions and this counterbalance has its limitations[30].

Even if not finally successful in resolving AU in our case, the active hormone calcitriol and its analog paricalcitol had some undeniable and visible effect on scalp and body hair – even as fur -, on eyebrows', and eyelashes' regrowth, indicating that vitamin D possesses an immunomodulating capability that interferes with the mechanism of disease in AA, opening the perspective of more powerful, less calcemic, and potentially more specific calcitriol analogs in the future. Thus, in addition to the cumulative evidence of vitamin D deficiency among alopecia patients, new therapeutic horizons in the complex management of this disease may be envisioned, especially now that newer more potent calcitriol analogues are being tested as anti-cancer and anti-metastatic agents. MART-10 for instance, has 3 times more VDR-binding affinity and much more resistance to CYP24A degradation compared to calcitriol, sparing the side effect of hypercalcemia[31].

CONCLUSION

Treatment with vitamin D in the form of cholecalciferol, as well the active hormone calcitriol and its analogs, such as the already marketed paricalcitol, may be envisioned for patients with AA/AT/AF, however with close monitoring of Ca metabolism parameters. Pilot clinical trials and RCTs are required to prove the effectiveness and safety of this therapeutic approach, as to establish the optimal form and dosage of vitamin D administration, alone or in combination with other treatments.

ACKNOWLEDGEMENTS

We thank Konstantinos Karkavitsas MD, Consultant Pediatric and Adult Dermatologist for his valuable contribution providing details on the previous history and treatments in P1 and P2, as well as for discussing with our multidisciplinary team our treatment modalities.

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